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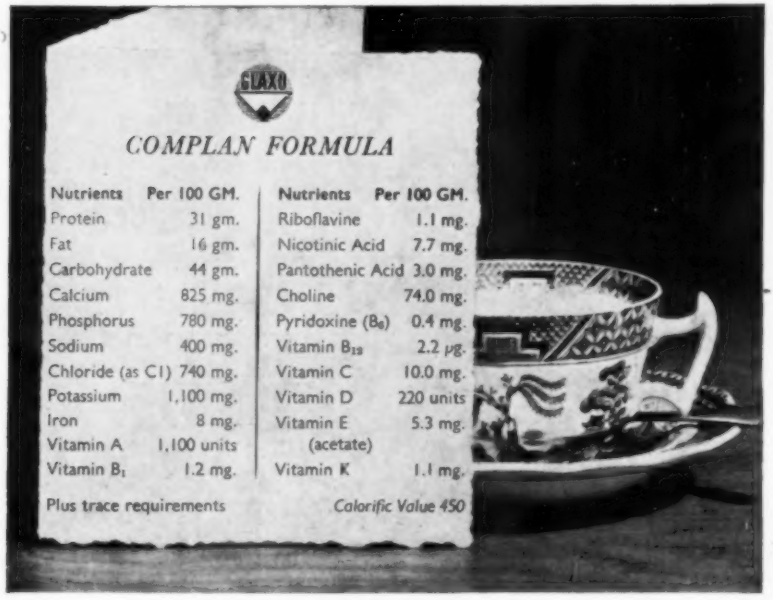

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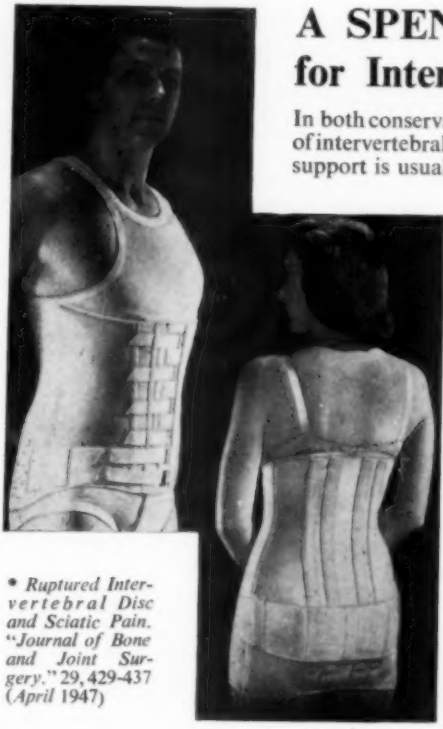

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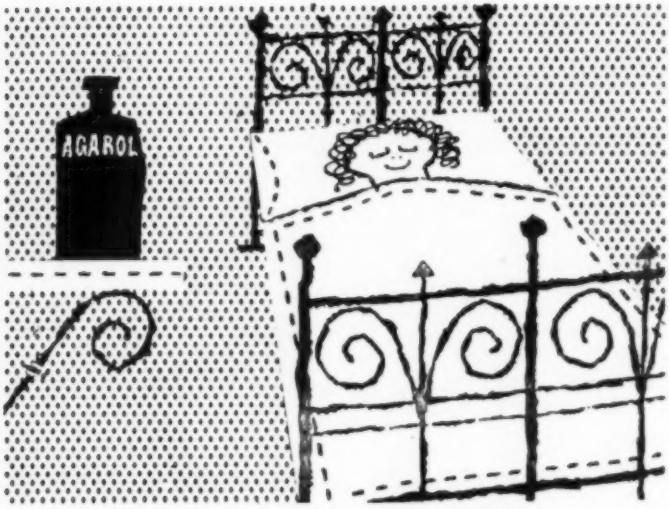

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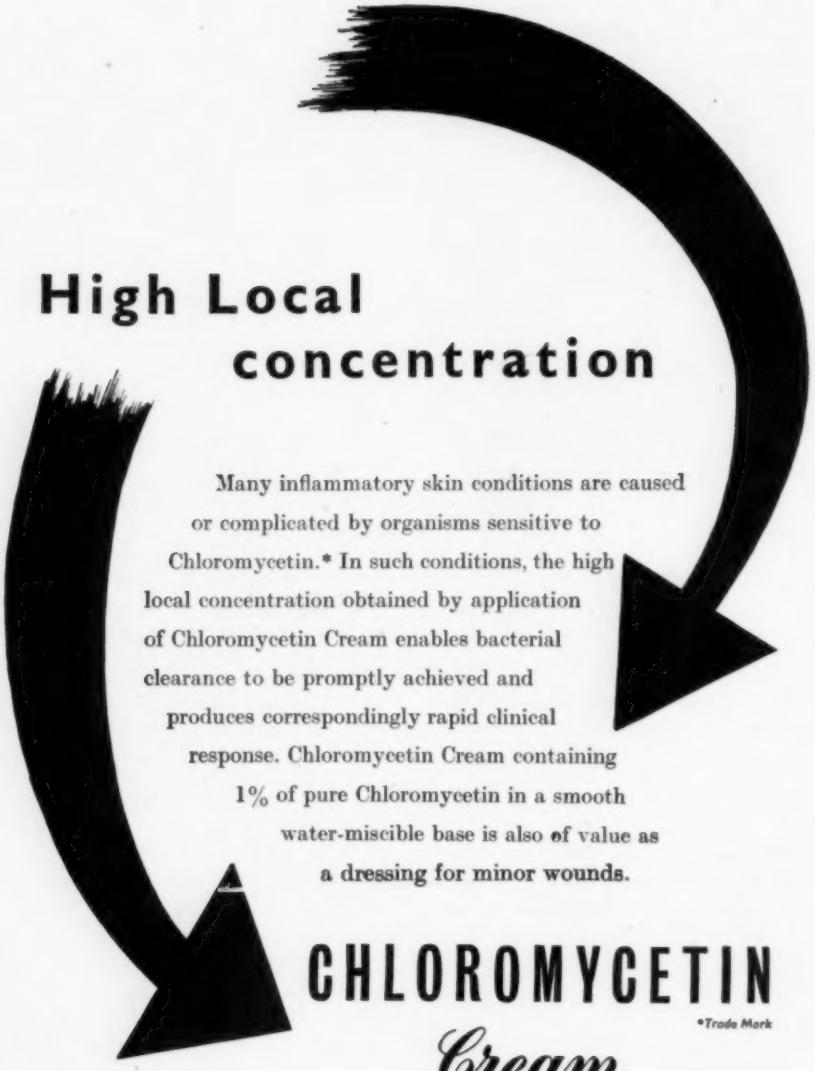

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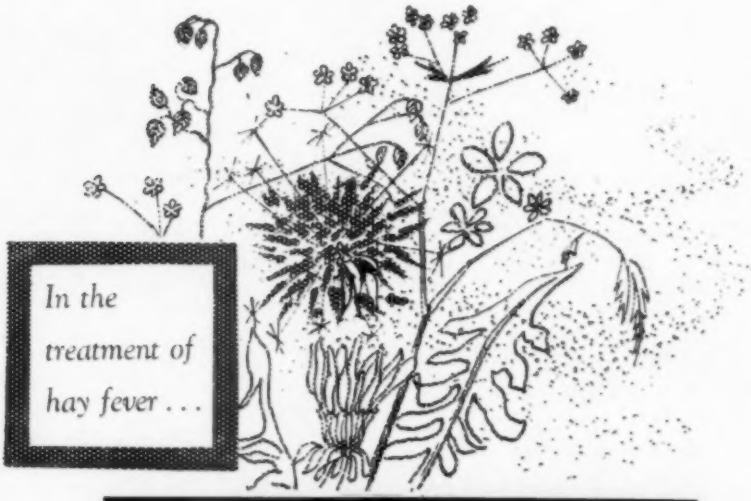

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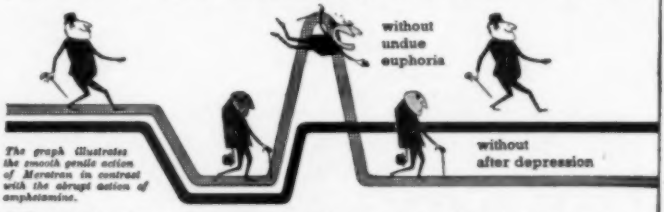

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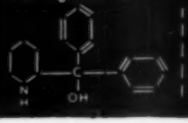


Merrell

COMPOSITION: 'MERATRAN' is available in pink tablets each containing 1 mg. pipradrol hydrochloride.

'MERATRAN' WITH RESERPINE tablets are white and each contains 1 mg. pipradrol hydrochloride and 0.25 mg. of reserpine. Each form is available in bottles of 30, 100 and 500 tablets.

Although a new drug, 'MERATRAN' has been extensively tested, and published reports cover its successful use in many hundreds of patients. Full details are given in the 'MERATRAN' booklet, a copy of which will be sent on request.

Meratran is a registered trademark of the Wm. S. Merrell Company, London

Distributed in Great Britain and Eire by

RIKER LABORATORIES LIMITED
LOUGHBOROUGH, LEICESTERSHIRE

Nothing so active is as that which least seems so

(Francis Thompson)

A peaceful countryside scene: but an active source of intense discomfort for all those susceptible to hay-fever, for now is the time of the year when invisible air-borne pollens begin to take their toll. Incapacitated by continual weeping, sneezing and nasal congestion, the hay-fever patient's desire for relief is understandably urgent; by the oral use of Benadryl* it can, in the great majority of cases, be promptly satisfied. In hay-fever, as in a variety of other allergic conditions, this powerful antihistamine provides a convenient and remarkably efficient means of controlling symptoms.

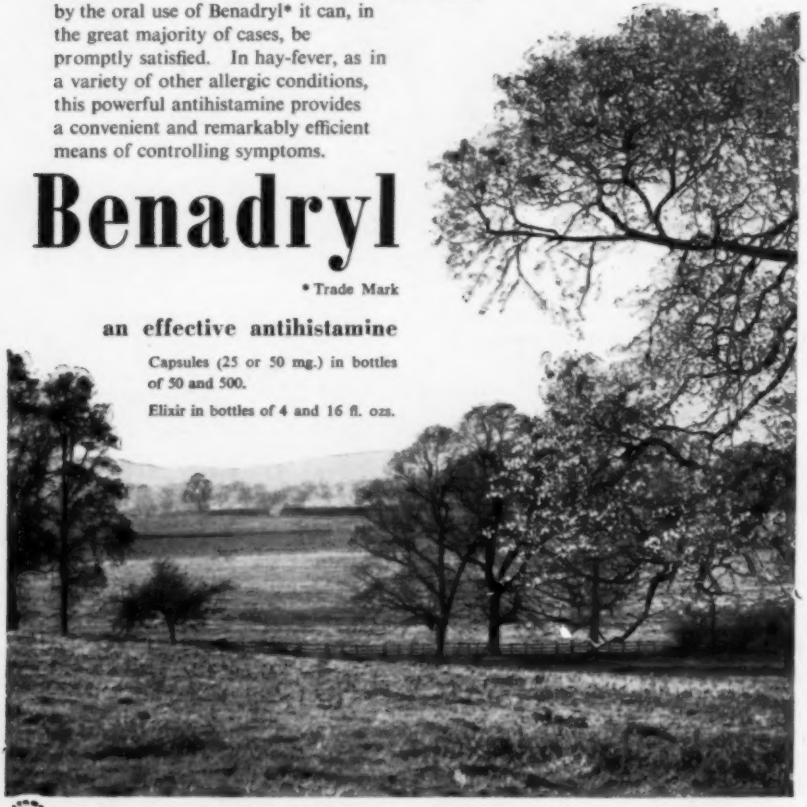
Benadryl

* Trade Mark

an effective antihistamine

Capsules (25 or 50 mg.) in bottles of 50 and 500.

Elixir in bottles of 4 and 16 fl. ozs.



PARKE, DAVIS & Co. Ltd. (*Inc. U.S.A.*), Hounslow, Middlesex. · Tel: Hounslow 2361

INTERNATIONAL STANDARD FOR HYALURONIDASE

An international standard for preparations of hyaluronidase has been established (World Health Organisation, Geneva, October 1955).

Hyalase—the first British preparation of hyaluronidase—was developed by Benger Laboratories and, in the absence of international agreement, a "Benger" unit was adopted and became widely accepted.

The strength of Benger 'Hyalase' ampoules remains unchanged (1000 Benger units) but will in future be decribed in terms of the new international unit.

Each ampoule of Hyalase contains 1500 international units.

HYALASE

Hyaluronidase

Hyalase ampoules (1500 international units) are available in boxes of 5, 20 and 100.

A PRODUCT OF BENGER RESEARCH

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE · ENGLAND

Pasteurised milk

Boiled milk.

INVALID DIET

Benger s Food—predigested for 5 minutes.

Benger's Food—predigested for 15 minutes.

MILK IS A readily available source of protein. Frequently, however, the patient is intolerant of the normal formation of curds in the stomach. Intake is reduced, digestion impaired and absorption of protein diminished.

A CLEAR CASE FOR BENGER'S FOOD. Benger's is a wheaten flour preparation containing the natural digestive enzymes *amylase* and *trypsin*. These "predigest" two vital foods — milk and wheaten flour. When hot milk is added to Benger's, the enzymes start to work—converting Benger's wheaten base into nourishing food and modifying the milk so that it does not form tough, indigestible curds in the stomach. Extra protein is thus absorbed by the patient without strain on the digestion. Moreover, the degree of "predigestion" can be regulated to suit the patient's condition—"nursing" him or her back to the point where normal diet can be ingested.

THE MICROPHOTOGRAPHS ABOVE, illustrating the effects of gastric juice on both milk and Benger's Food, show how Benger's prevents the formation of curds.

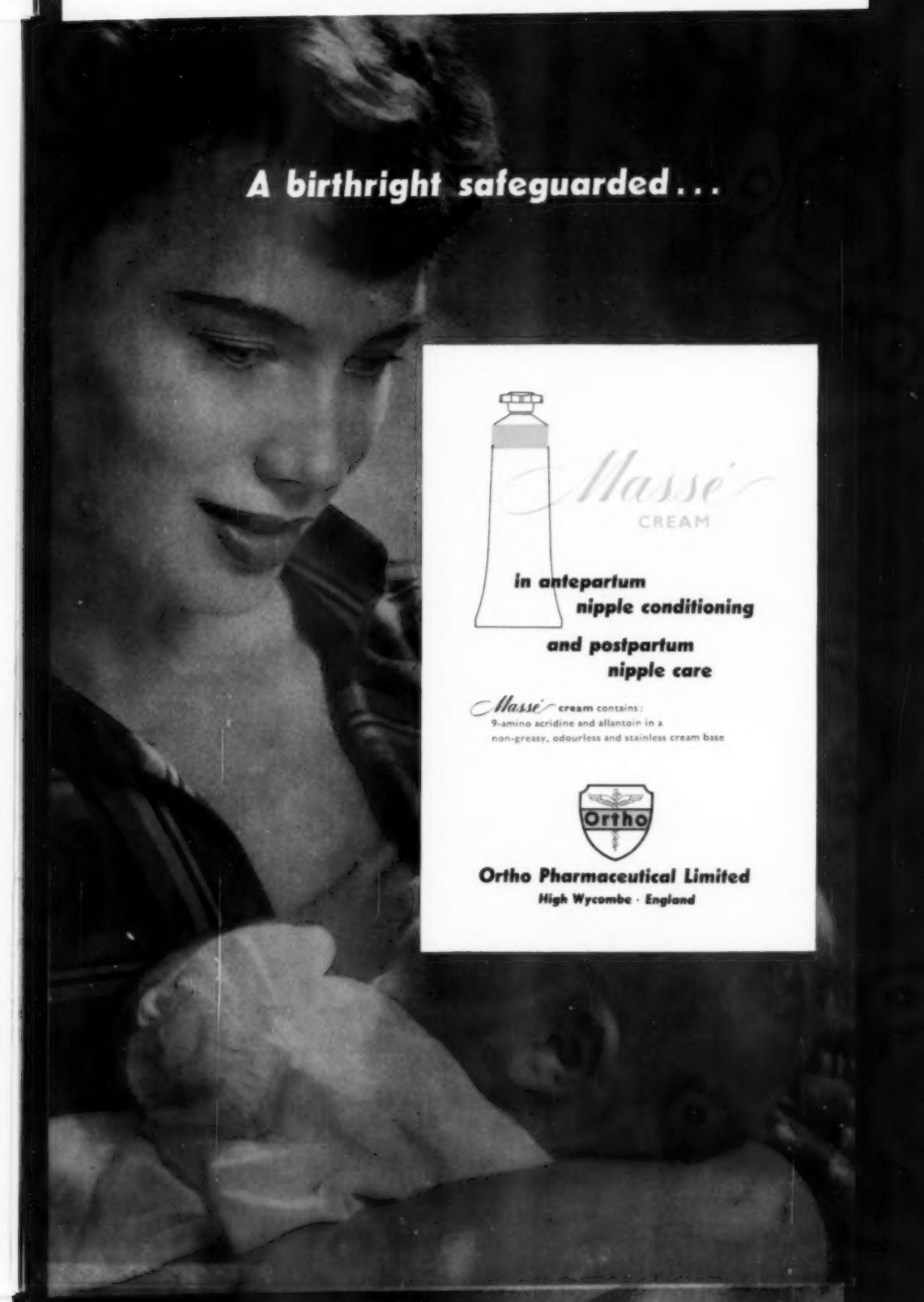
FULLY DESCRIPTIVE LITERATURE, including a specially-prepared Invalid Diet Recipe Book, is available; and a Technical Information Service is always at your disposal.

A clear case for BENGER'S FOOD

E. 3

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE

A BENGER PRODUCT


A birthright safeguarded . . .
Massé
CREAM
in antepartum
nipple conditioning
and postpartum
nipple care
Massé cream contains:
9-amino acridine and allantoin in a
non-greasy, odourless and stainless cream base
Ortho
Ortho Pharmaceutical Limited
High Wycombe · England

Clean hands

Adequate washroom facilities are essential to combat disease in the hospital, factory and office—and vital for clean food. Sometimes the demand is for large quantities of hot water continuously, day and night—or maybe it is needed instantaneously at irregular times. But whatever the hot water requirement, the Heating Engineers at your Area Gas Board have had considerable experience in fitting thousands of different hot water installations and will gladly advise you on your problem.

WHATEVER YOUR BUSINESS—**The Gas Industry appreciates the needs of individual consumers for prompt service and for advice which accords with the customer's special circumstances and requirements. Each Area Gas Board offers efficient service to users of gas-fired equipment and can give expert advice based upon the pooled knowledge of all the Boards and of gas users in other countries**

—CONSULT YOUR AREA GAS BOARD

ISSUED BY THE GAS COUNCIL

THE GAS INDUSTRY MAKES THE BEST USE OF THE NATION'S COAL

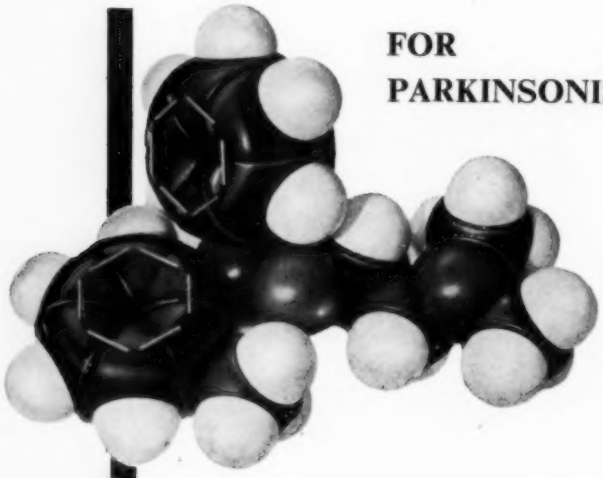
Zicthol

A cream containing 16% zinc oxide, 4% ichthammol and 2% camphor in a soothing, drying base, for use at the sub-acute stage when a little weeping may still be present but the area is mainly crusted, irritant and sore. Basic N.H.S. cost 2/- for 1 oz tube, 3/- for 2 oz tube.

Pixcyl

A cream containing purified fractions equivalent to 5% crude coal tar, 1% salicylic acid and 25% zinc oxide in a non-drying base, for use at the chronic stage. This is safer than the customary coal tar preparation. Basic N.H.S. cost 2/3 for 1 oz tube.

GENATOSAN LTD. *Loughborough, Leicestershire.*



FOR PARKINSONISM

DISIPAL

β-Dimethylaminoethyl-2-methylbenzhydrylether Hydrochloride. B.S. 5930

FOR THE SIMULTANEOUS TREATMENT OF THE PHYSICAL AND PSYCHICAL SYMPTOMS

Clinical trials carried out in Great Britain and throughout Europe have established Disipal as a very effective treatment of Parkinsonism.

- *British Medical Journal*, 1955, **2**, 352.
- *Arzneim. Forsch.*, 1955, **5**, 72-73.
- *Ned. Tijdschr. v. Geneesk.*, 1955, **99**, 1103.
- *Geneesk. Gid.*, 1955, **33**, 302.

Packs: ***Bottles of 100 and 250 x 50 mg. Tablets.***
May be prescribed on Form E.C. 10.

Made under Licence from:—

BROCADES

N.V. KONINKLIJKE PHARMACEUTISCHE FABRIEKEN V/H
BROCADES-STHEEMAN & PHARMACIA
AMSTERDAM - NETHERLANDS

by CAMDEN CHEMICAL COMPANY LTD.
61 GRAY'S INN ROAD LONDON, W.C.1.

Sole Agents for the United Kingdom, from whom literature and samples may be obtained on request.

Disipal is distributed in Eire by Messrs. Dominick A. Dolan, 58 Bolton Street, Dublin.

*U.K. Patent Nos. 722009, 585994, 607258 and 743495.

Other Patents pending.

appetite must be controlled

Fat people die first — as any insurance company knows.
To live longer, they must eat less.
'Dexedrine' is the safe, *effective* drug for the control of appetite in weight reduction. 'Dexedrine' not only makes it easier for the patient to eat less, but also prevents the irritation and depression that so often accompany the start of a reducing regimen.

Dexedrine — safe, *effective* appetite control

Smith Kline & French
represented by Menley & James, Limited, Coldharbour Lane, London, S.E.5
Samples and literature available on request

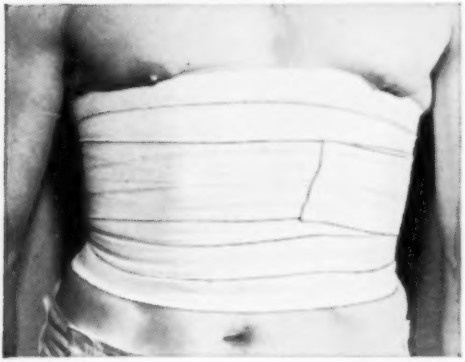
DP66(Col)

Elastoplast Bandaging Technique

in the treatment of

Fractures

In certain types of fracture it may be impossible or unnecessary to obtain fixation by plaster of Paris splinting. Such fractures can often receive adequate support and immobilisation by the application of Elastoplast.



FRACTURED RIBS

Pain produced by respiratory movement may be relieved by applying long strips of Elastoplast well over and beyond the site of the fracture. Moderate tension should be used and the application carried out with the chest held in the position of expiration.

Other similar uses

FRACTURED CLAVICLE *prevention of overriding of fragments resulting from weight of limb and muscle action.*

FRACTURED PATELLA *pending operation, the fragments are prevented from becoming widely separated.*

FRACTURED MANDIBLE *for external support after reduction of fracture-dislocation.*

Elastoplast elastic adhesive bandages (Porous) B.P.C. are available in 3 yard lengths and 2″, 2½″, 3″ and 4″ widths prescribable on Form E.C.10.
Outside the British Commonwealth Elastoplast is known as Tensoplast.

FULL DETAILS FROM SMITH & NEPHEW LTD · WELWYN GARDEN CITY · HERTS

S&N

A SHOOTING PARTY AT LUNCH

This picture, by an unknown illustrator, recalls the large outdoor compositions of Watteau, which it resembles in revealing the Eighteenth-Century French preoccupation with extravagant al fresco *gatherings.*

One looks in vain for any evidence that the "shooting" has produced results. Of the social success of the consequent junketings, however, there can be no doubt at all.

Eating Out...

Eating away from home is always more or less hazardous to the hyperacid patient.

Portable medication is, in the patient's untutored hands, scarcely less risky; indiscriminate use of the many alkaline remedies within easy purchase often does more harm than good.

For the occasional or habitual dyspeptic alike, PRODEXIN affords, in a convenient and palatable tablet, a means of checking hyperacidity by regulating gastic *p*H at a safe and constant level for long periods.

PRODEXIN

Each Prodexin Tablet contains:

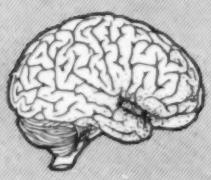
Aluminium glycinate ..... 0·9 gm.
Light magnesium carbonate ..... 0·1 gm.

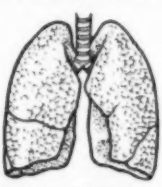
Packings: Cartons of 30 individually wrapped tablets and dispensing packs of 240 tablets.
Basic N.H.S. cost of 240 tablets: 30s. 4d.

C. L. BENCARD LTD., PARK ROYAL, LONDON, N.W.10

Selective amine for asthma . . .

with only $\frac{1}{16}$ the central nervous system effect of ephedrine, Orthoxine avoids wakefulness and excitation, permits the asthmatic patient to rest and relax.





with twice the broncho-dilating effect of ephedrine, Orthoxine eases laboured respiration, provides more air for the asthmatic.

with only $\frac{1}{2000}$ the pressor effect of adrenaline, Orthoxine may be used even in elderly asthmatic patients and those with coexistent hypertension or cardiac disease.

ORTHOXINE* HYDROCHLORIDE

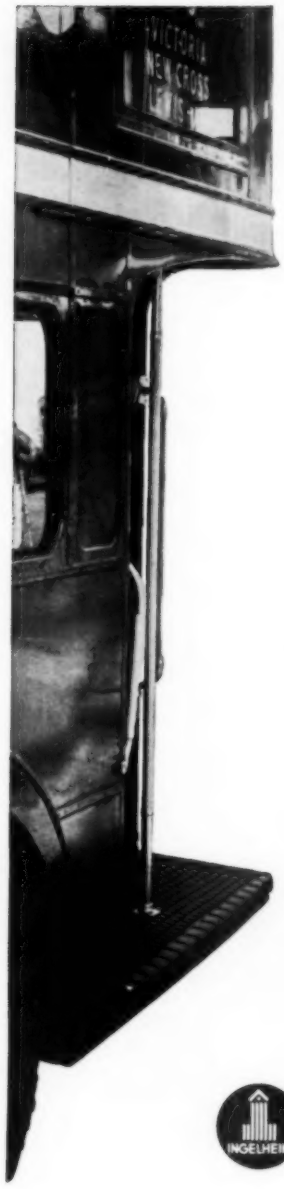
DOSAGE:
Adults—½ to 1 tablet repeated, if required, every three or four hours. Children—fractional doses according to age.

SUPPLIED:
Tablets of 100 mg. in bottles of 25 and 100.

* Regd. Trade Mark for the Upjohn brand of methoxyphenamine

Upjohn Fine Pharmaceuticals since 1886

UPJOHN OF ENGLAND LTD., 4 Aldford Street, Park Lane, London, W.1, England



reducing the risk of reducing...

PRELUDIN

brand of 2 - phenyl - 3 - methyl - tetrahydro - 1, 4 - oxazine - hydrochloride

PRELUDIN—the appetite controlling agent that does not raise the blood pressure

PRELUDIN, because it has no significant effect on the circulatory system, is the safest possible weight-reducing treatment for *all* obese patients—particularly those with cardiovascular disorders or hypertension. Here, for the first time, is a powerful appetite controlling agent that depresses the appetite, breaks the psychogenic overeating habit, and controls food intake without serious side effects. It enables the patient to lose weight safely and without mental strain by strengthening adherence to a prescribed diet. PRELUDIN does *not* create excessive mental stimulation. It is the prescription of choice in all cases of obesity—especially those with cardiovascular disorders—because it reduces the risk of reducing.

Preludin—the safe prescription for obesity

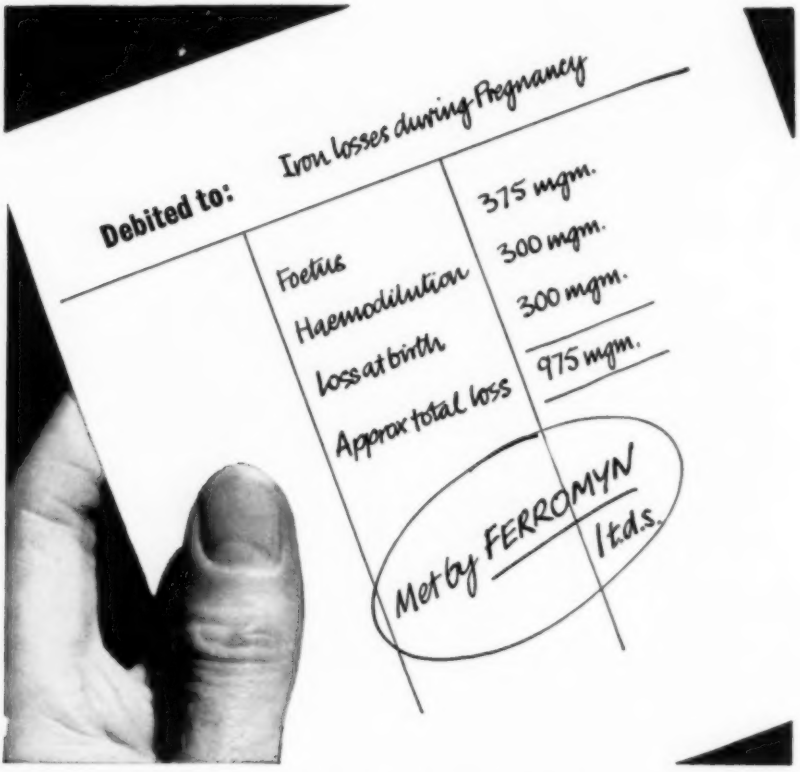
INGELHEIM

Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent, for

C. H. Boehringer Sohn, Ingelheim am Rhein

Registered proprietors of the trade mark.

**Regd. Trade Mark*



PREGNANCY: meeting the inevitable iron deficiency

Progressive inroads are made on the maternal iron stores during pregnancy. The demand made is greatly increased during the third trimester, and there is little doubt that the exposition of a suitable form of iron is of definite clinical value. FERROMYN meets these important demands because it affords maximum bivalent iron from a minimum of ferrous salt, does not cause alimentary upset, has a high utilisation factor and will maintain a satisfactory haemoglobin level throughout term.

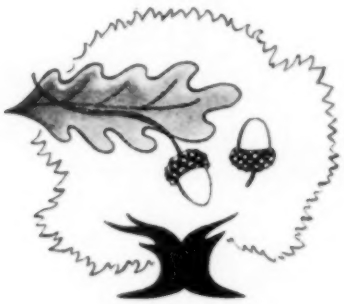
FERROMYN is supplied in four forms: **FERROMYN TABLETS** Each tablet contains: *Ferrous Succinate* 150 *mgm.* **ELIXIR FERROMYN** Each teaspoonful contains: *Ferrous Succinate* 150 *mgm.* **FERROMYN 'B' TABLETS** Each tablet contains: *Ferrous Succinate* 150 *mgm. Aneurine Hydrochloride* 1 *mgm. Riboflavin* 1 *mgm. Nicotinamide* 10 *mgm.* **ELIXIR FERROMYN 'B'** Each teaspoonful contains: *Ferrous Succinate* 150 *mgm Aneurine Hydrochloride* 1 *mgm. Riboflavin* 1 *mgm. Nicotinamide* 10 *mgm.*

FERROMYN

CALMIC LIMITED, CREWE. Phone Crewe 3251-5 **LONDON:** 2 Mansfield St., W.1. Phone LANgham 8038-9
AUSTRALIA: 458-468 Wattle Street, Ultimo, Sydney, N.S.W. **CANADA:** Terminal Buildings, York St., Toronto.

. . . leadership in oral-iron therapy

F2



. . from little acorns grow

Cremalgin rubefacient balm was first introduced in August, 1954.

Since then, more than a quarter-million ounces have been prescribed on E.C.10.

By making every possible use of the most modern and efficient production methods, Cremalgin was one of the first products to introduce a substantial economy into the National Health Service without a shadow of compromise in standards.

The "little acorn" has grown into a very large "oak" indeed. For Cremalgin now makes an important reduction in the cost of the ever growing demand for rubefacient balms for the treatment of muscular rheumatism and allied conditions.

Methyl Nicotinate 1.0%
Glycol Salicylate 10.0%
Histamine Dihydrochloride 0.1%
Capsicin 0.1%
Excipient q.s.

Cremalgin

Rubefacient Balm.

WEST PHARMACEUTICAL COMPANY

WOOD LANE, LONDON, W.12. Telephone: SHEpherds Bush 6262

A NEW ORAL CHEMOTHERAPEUTIC FOR TUBERCULOSIS

A new chemical compound formed by the combination of INH and PAS in molecular proportions

DIPASIC IS AVAILABLE FOR INVESTIGATION

LITERATURE ON THERAPY AND DOSAGE ON REQUEST

DIPASIC

TABLETS OF 100 mg. OF ISONICOTINIC ACID HYDRAZIDE-P-AMINOSALICYLATE

GEWO

BENGUE & Co. Ltd. *MANUFACTURING CHEMISTS*

MOUNT PLEASANT - ALPERTON - WEMBLEY - MIDDLESEX

Bengue & Co. Ltd. make "Dipasic" available in the United Kingdom by arrangement with Ed. Geistlich Sons Ltd., Wolhusen (Switzerland).

The right diet at your fingertips

This filing box, designed for the consulting room desk, contains an indexed supply of diet cards for 16 different conditions. The cards are planned to include specimen daily menus which facilitate the patient's co-operation and save the doctor's time. This is one of the services offered free of charge to the medical profession by the Energen Dietary Service.

In special cases, clinical considerations often necessitate the preparation of a diet which takes into account the individual requirements of the patient. On receipt of appropriate information from the practitioner, such diets can be specially constructed and sent through the post; or a consultation can be arranged with a senior dietitian.

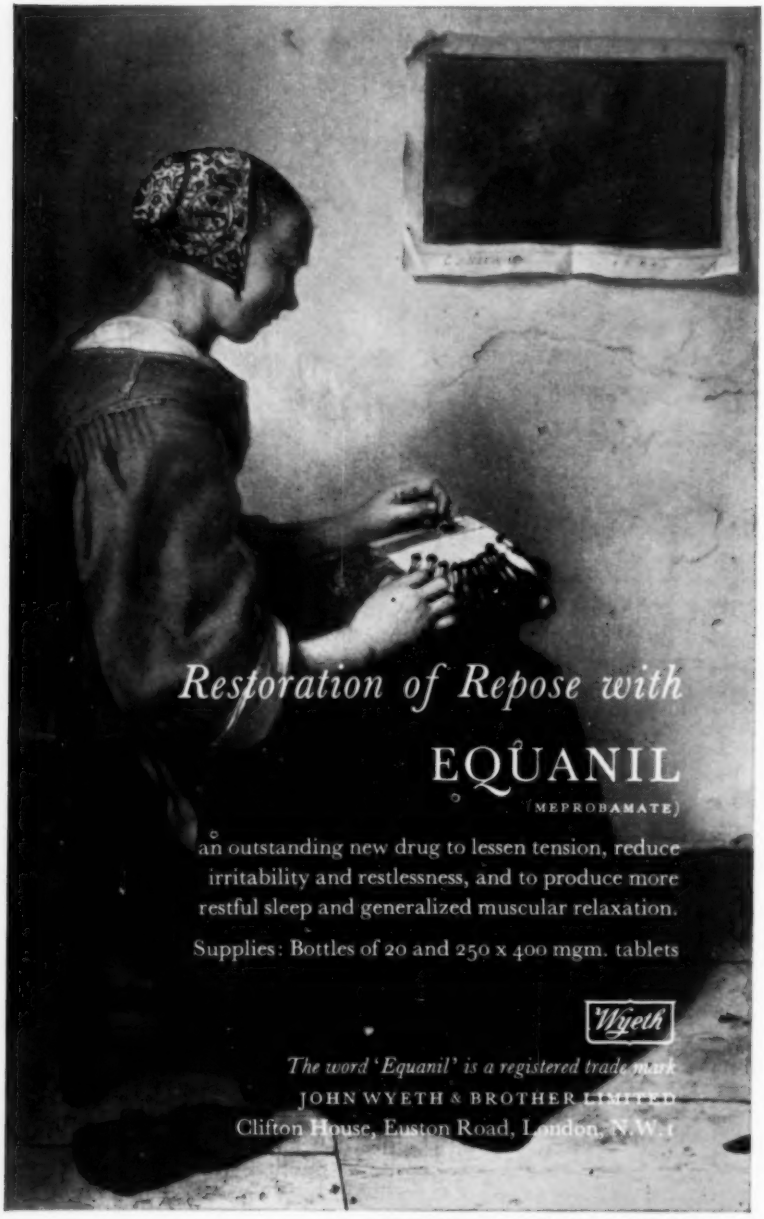
The Energen Dietary Service is staffed by fully qualified dietitians, under close medical supervision. It offers independent information and assistance to the medical profession in all dietary and nutritional matters.

Requests for the Diet Card Filing Box, or other inquiries should be addressed to:

THE HEAD DIETITIAN, ENERGEN DIETARY SERVICE,
25A, BRYANSTON SQUARE, LONDON, W.1.
TELEPHONE: AMBASSADOR 9332

ENERGEN DIETARY SERVICE

AVAILABLE ONLY IN THE UNITED KINGDOM


Restoration of Repose with
EQUANIL
(MEPROBAMATE)
an outstanding new drug to lessen tension, reduce irritability and restlessness, and to produce more restful sleep and generalized muscular relaxation.
Supplies: Bottles of 20 and 250 x 400 mgm. tablets
Wyeth
The word 'Equanil' is a registered trade mark
JOHN WYETH & BROTHER
Clifton House, Euston Road, London, N.W.1

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Moniliasis

(VULVOVAGINAL CANDIDIASIS)

its simple diagnosis . . .

NICKERSON'S MEDIUM

isolates candida growth readily visible.

Available in packages of six vials complete with sterile cotton swabs.

CANDIDA

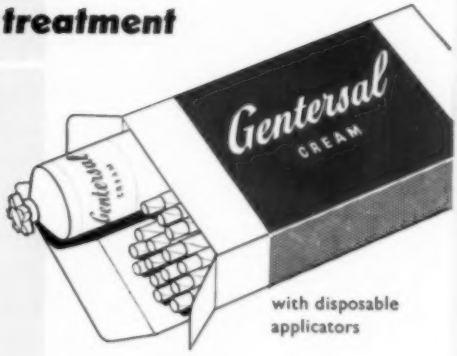
and NEW effective treatment

Gentersal

CREAM

rapid response
less irritating
less staining

* gentian violet 0·05% and alkyldimethyl-benzylammonium chloride 0·05%



with disposable applicators

LITERATURE ON REQUEST

Ortho

Ortho Pharmaceutical Limited · High Wycombe · England

The secret of sleep...

in a capsule

Lilly **BARBITURATES**

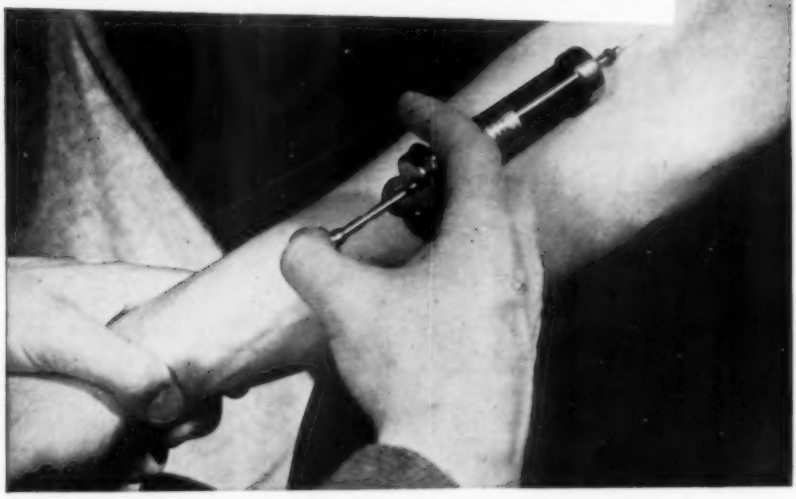
'SECONAL SODIUM'
Quick onset - short duration.
In 'Pulvules' ¾ gr. and 1½ grs.

'SODIUM AMYTAL'
Medium onset and duration.
In 'Pulvules' 1 gr. and 3 grs.

'TUINAL'
Quick onset - medium duration.
In 'Pulvules' 1½ grs. and 3 grs.

ELI LILLY & COMPANY LIMITED, BASINGSTOKE, ENGLAND

INTRAVENOUS IRON...



WHEN THE INTRAVENOUS route is preferred, Ferrivenin commends itself because:—

* The absorption and utilization of its iron content are virtually total.

* The response in true iron-deficiency anaemia is related directly to the amount given.

* Since its introduction in 1947 it has enjoyed the confidence of physicians throughout the world.

AMPOULES OF FERRIVENIN contain 100 mg. of iron (as saccharated iron oxide) in 5 ml.; boxes of 5, 10 and 50 ampoules are available.

FULLY-DESCRIPTIVE LITERATURE is available on request, and a Technical Information Service is at your disposal.

FERRIVENIN REGD

L2

BENGER LABORATORIES LTD · HOLMES CHAPEL · CHESHIRE

A BENGER PRODUCT

INTRAMUSCULAR ADMINISTRATION OF IRON IN PREGNANCY

THIS WOMAN is six months pregnant. It will be her fourth child. Increased intake of iron is essential on account of foetal demands. It is even more important in repeated pregnancies since the equivalent of 750 mg. iron may be lost with each pregnancy.

A CLEAR CASE FOR IMFERON, new iron-dextran complex. Imferon is the first safe and effective intramuscular iron. It will restore the haemoglobin concentration rapidly and reliably. Brit. Med. J. 1954, *2*, 1257.

FULLY-DESCRIPTIVE LITERATURE is available and a Technical Information Service is always at your disposal.

A clear case for **IMFERON** IRON-DEXTRAN COMPLEX
TRADE MARK

A PRODUCT OF BENGER RESEARCH

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE

" No — there's a big difference, Mr. Baxter . . .

. . . as you will remember, in protamine zinc insulin, the action of the insulin is modified by the presence of a foreign protein, protamine. In contrast, I.Z.S. contains no protein or peptide material other than the insulin itself. That is its great advantage over other insulins. You see, gentlemen, the action of I.Z.S. persists for the required period by appropriate adjustment of the particle size of the insulin zinc compound. It is because the effect of I.Z.S. is entirely independent of any modifying protein, that allergic reactions following its use are virtually unknown. Any other questions ? "

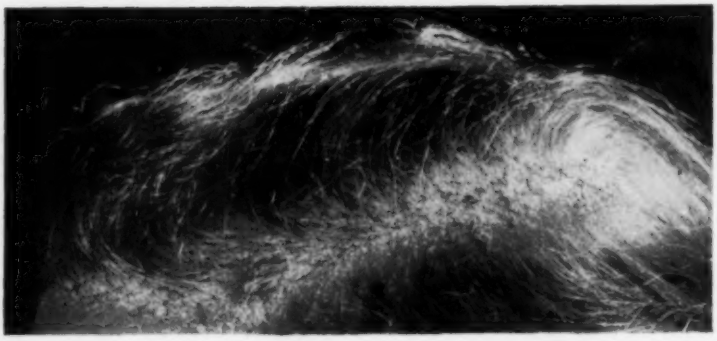
I.Z.S. A.B. Vials of 10 c.c. 40 or 80 units per c.c.
I.Z.S. (Amorphous) A.B. Vials of 10 c.c. 40 or 80 units per c.c.
I.Z.S. (Crystalline) A.B. Vials of 10 c.c. 40 or 80 units per c.c.

Insulin Zinc Suspension A.B.

Joint Licensees and Manufacturers :
ALLEN & HANBURYS LTD LONDON E2 • THE BRITISH DRUG HOUSES LTD LONDON N1

Effective Double Treatment

for Dandruff, Seborrhoea Capitis and Scalp Psoriasis



Sebigen

Sebigen — formerly known as Sebbix Cream — is an effective, white, virtually odourless cream. Non-greasy, it is readily used by women since it does not mat or clog the hair.

Purified fraction equivalent to

Crude Coal Tar	10%
Sulphur	3%
Salicylic Acid	2%

in a water miscible base.

1-oz. tube — 2/3d. basic N.H.S. price.

Genisol

Genisol is a new shampoo type preparation intended for the removal of scale and stimulation of normal skin growth. Genisol can be used with Sebigen or by itself when treating mild seborrhoea and dandruff.

Purified fraction equivalent to

Crude Coal Tar	2%
Hexachlorophene	1%

2-oz. bottle (approx. 8 shampoos) — 2/0d. basic N.H.S. price.

Safe · effective · economical

GENATOSAN LIMITED, LOUGHBOROUGH, LEICESTERSHIRE

A neutral, stable and soluble theophylline derivative

NEUTRAPHYLLINE

7-(2:3-Dihydroxypropyl) theophylline

Ampoules, tablets and suppositories
Active and well tolerated by mouth or per rectum
Completely painless when injected intramuscularly

Bronchospasm : Cardiac and Renal Oedema : Coronary Insufficiency

CONTINENTAL LABORATORIES LIMITED
101 Great Russell Street, London, W.C.1.

MARMITE
yeast extract

in General Nutrition

The need for a well-balanced diet is generally recognised as being essential for good health. Certain authorities suggest that in some diets to-day there may be a slight shortage of the B_2 vitamins. Since it contains important vitamins of this group, Marmite is often recommended when a deficiency is suspected, or as a routine measure to guard against such deficiencies.

in Paediatrics

Marmite is a particularly useful source of the B_2 vitamins for administration to children, who take to it readily.

in Tropical Medicine

Vitamin B_2 deficiencies are often encountered in tropical countries and Marmite has proved to be exceptionally useful in such disorders. Its value in the treatment of retrobulbar neuritis is of special interest.

Literature on Request

Obtainable from chemists and grocers

Special terms for packs for hospitals, welfare centres and schools

MARMITE LIMITED, 35 SEETHING LANE, LONDON, E.C.3

5310

Diagnosis: Obstinate eczema of the face. Photograph taken before treatment with "F99."

Photograph taken after 18 weeks' treatment with one "F99" capsule and one application of "F99" ointment daily.

℞ F99 for

OINTMENT
CAPSULES
LIQUID

ECZEMA
VARICOSE ULCERS
FURUNCULOSIS etc.

It has been shown beyond question by large scale serum-lipids studies that a good proportion of patients suffering from intractable skin conditions have a deficiency of the essential fatty acids. It is not possible to carry out these studies in everyday practice, but any patient with eczema or furunculosis who fails to respond to symptomatic treatment should most certainly be tried with essential fatty acids "F99." A high proportion of these patients will be found to respond.
In gravitational ulcers, where the skin is "under-nourished," the application of additional essential fatty acids rarely fails to heal the wound.

Literature on request

INTERNATIONAL LABORATORIES LTD., *Dept. PR38*, 205 HOOK ROAD, CHESSINGTON, SURREY

'Specifically recommended'
for **DANDRUFF**

FORMULA	
Cetyl Alcohol	15.6%
Cetrimide B.P.	15.6%
Lanolin B.P.	1.0%

SEBODERM contains 15.6% of CETRIMIDE B.P. the quaternary ammonium compound that has been found to be most effective in the treatment of dandruff. Its regular use ensures complete control.
Lanolin is incorporated into the finely-emulsified base, thus ensuring freedom from scalp irritation.
In cases of Seborrhoeic dermatitis SEBODERM is an extremely effective adjunctive treatment.

Literature and professional sample will gladly be sent on request.

...**SEBODERM**
CETRIMIDE SHAMPOO

PRIORY LABORATORIES LTD., PYRAMID WORKS, WEST DRAYTON, MIDDLESEX

AMPHETONE
REGISTERED

A GENERAL STIMULANT FOR THE CENTRAL NERVOUS SYSTEM

For cases requiring a quick-acting general stimulant without increasing the patient's appetite, we consider Amphetone unique. It combines for the first time, Dexamphetamine Sulphate and Strychnine with Glycerophosphates and members of the Vitamin B Group. The Dexamphetamine provides the convalescent with an immediate feeling of well-being, this being followed by the well-known tonic effects of the other medicaments. Clinical reports have been excellent.

FORMULA Dexamphetamine Sulphate B.P.C., 1/12 grain: Strychnine Hydrochloride B.P., 1/60 grain: Calcium Glycerophosphate B.P.C., 2 grains: Sodium Glycerophosphate B.P.C., 2 grains: Aneurine Hydrochloride B.P., 1/30 grain: Nicotinamide B.P. 1/4 grain: Riboflavine B.P. 1/60 grain: Syrup of Blackcurrant B.P.C., 2 fluid drms.: Water, to 1/2 fluid ounce.

POISON | S4

Available in bottles containing 10, 20, 40, and 80 fluid ounces. Professional prices 4/8, 8/10, 14/7 and 26/5 each. Samples available on request.

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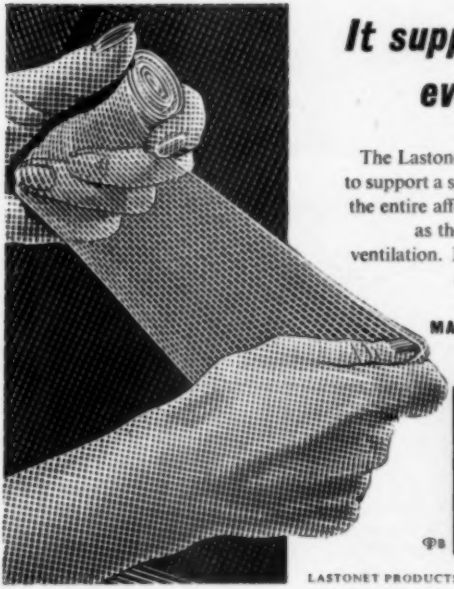
(Incorporating J. C. Arnfield & Sons, Ltd.)

WA1



It supports evenly, everywhere

The Lastonet bandage has a two-way stretch to support a sprained or weak joint evenly over the entire affected area. It is also cool to wear as the lightweight net allows plenty of ventilation. In 5-yard lengths (fully stretched) and 2½, 3, 3½, 4 or 6 inch widths.

MAY BE PRESCRIBED UNDER THE NATIONAL HEALTH SCHEME

Lastonet
ELASTIC NET BANDAGE

PB

LASTONET PRODUCTS LTD, CARN BREA, REDRUTH, CORNWALL

Peptic Ulcer

...a Four-Fold LIQUID Medication

KOLANTYL has proved its great value as a complete ulcer therapy in tablet form. It is now also available, for those who prefer a liquid medication, as

Kolantyl Gel

containing in each 10 c.c.

'Merbentyl' (5 mg.)
an antispasmodic notably free from side-effects.

Aluminium Hydroxide Gel (400 mg.)
+Magnesium Oxide (200 mg.)
for complementary antacid effect.

Methylcellulose (100 mg.)
a protective demulcent.

Sodium Lauryl Sulphate (25 mg.)
a pepsin and lysozyme inhibitor.

In bottles of 12 fluid ozs.
DOSE: 2 to 4 teaspoonfuls (10-20 c.c.) three or four times daily.

Merrell

Distributed in the United Kingdom and Eire by
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for the Wm. S. Merrell Company, London.

180
WATERPROOF
dressings
in the
DALMAS
Doctor's Cabinet

DALMAS waterproof dressings provide safe and speedy first-aid for all wounds, cuts and common casualties. Self-adhesive, they are simple to apply and flex with every movement like a second skin. The special Doctor's Cabinet contains 180 dressings in seven sizes and shapes together with a spool of Dalmas Strapping. Fully descriptive literature will be sent on request.

DALMAS LIMITED, LEICESTER & LONDON Established 1823 MS/A

LIL-LETS

the new vaginal tampon without applicator

A tampon which has been successfully marketed on the Continent during the last five years has now become widely accepted in this country under the name LIL-LETS.
Following extensive clinical trials, LIL-LETS have won the support of leading gynæcological opinion. Samples will gladly be sent to medical practitioners on request.

LIL-LETS
o.b.

LIL-LETS have these main advantages:

LIL-LETS need no applicator. By inserting the tampon with the fingers, the risk of bruising is eliminated.

LIL-LETS assist personal hygiene. At 1/6 for 10 they are so much cheaper than other leading tampons that women will be encouraged to change them often. They are easily carried about and easily disposed of.

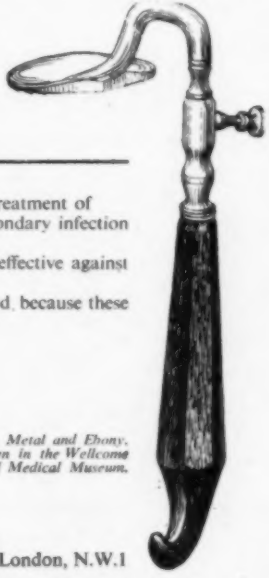
LIL-LETS are highly absorbent. They absorb almost ten times their own weight in moisture and swell sideways, not lengthways. They are, therefore, really safe.

LIL-LETS are individually wrapped. Each tampon is sealed in a transparent cover. There is no risk of soiling or infection when it is carried loose.

S&N LILIA LTD · LOMESHAYE MILL · NELSON · LANCS

For sore throats

Bacitracin . . .
Polymyxin . . . Neomycin Troches



Streptets are new triple antibiotic troches for the local treatment of superficial oral infections and for the prophylaxis of secondary infection in oral and dental surgery.
The three contained antibiotics are safe to use and are effective against a wide range of bacteria.
Toxic manifestations and drug-resistance are rarely caused because these chemotherapeutic substances are poorly absorbed.

Streptets are supplied in bottles of 20 troches.

Streptets

Tongue Depressor, Metal and Ebony. From a specimen in the Wellcome Historical Medical Museum.

Wyeth

The word 'Streptets' is a registered trade mark
John Wyeth & Brother Ltd., Clifton House, Euston Road, London, N.W.1

SANCTIONED ON N.H.S. PRESCRIPTIONS (FORM E.C.10)

EPHAZONE tablets

The rational, symptomatic remedy for bronchial spasm in

ASTHMA & BRONCHITIS

CONTAINING IN EACH TABLET:
Ephedrine ¼ grain
Theobromine ½ grain
Phenazone 1 grain
Calcium gluconate ½ grain

THIS PREPARATION IS NOT ADVERTISED TO THE GENERAL PUBLIC

EPHAZONE LTD 59 BROOK STREET, LONDON, W.1

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"MIOTROL"-P
TRADE MARK

Tablets containing :—Methyltestosterone 2.5 mg. Ethinyl Oestradiol 0.005 mg. Phenobarbitone 16.0 mg. (¼ gr.)

A synergistic combination of androgen and oestrogen with phenobarbitone.

Specifically designed for control of symptoms associated with menopausal disturbances, premenstrual migraine and tension, dysmenorrhoea.

Literature forwarded on request.

AN OXOID PRODUCT

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ENCYNEX

For the treatment of

RHEUMATOID ARTHRITIS
MUSCULAR RHEUMATISM
ACUTE RHEUMATIC FEVER
SUBDELTOID BURSITIS
FIBROSITIS

ENCYNEX consists of coated tablets each containing :

p - Aminobenzoic acid	32·5 mg.
Sodium salicylate	150·0 mg.
Sodium bicarbonate	60·0 mg.
Acetophenetidin	150·0 mg.

May now be prescribed on Form E.C.10
N.H.S. basic cost : 50 tablets 3/4d.
(2/10d. when ex dispensing pack)

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. . . I've great faith in these Dalmas Tulle Gras Dressings

DALMAS TULLE GRAS DRESSINGS.

PETRONET
Paraffin Gauge Dressing B.P.C.

SULPHONET.
Impregnated with 5% sulphathiazole — sterile non adherent dressing for rapid healing and painless removal. Packed in convenient 3½" squares singly or in boxes. Prescribable on E.C. 10 forms. Or as a continuous strip.

URO-SULPHONET.
A strip dressing 3½" × 5 yds. Impregnated with a wool alcohol emulsion containing 5% sulphathiazole and 2% urethane — bacteriostatic and analgesic, destroys offensive wound odours and an ideal burn dressing.

Petronet and Sulphonet are available on E.C.10

M4/A

DALMAS Non-stitch DUMB-BELL SUTURES

A professionally approved method, used with or in place of normal stitching. Easy to apply and self-adhesive, they keep the edges of the wound pressed firmly together. In packs of 6 dozen, ready for use.

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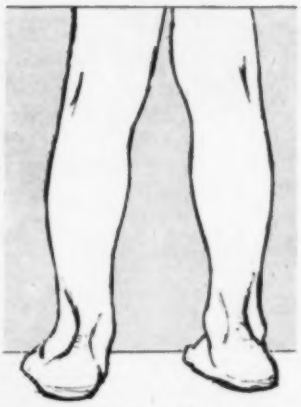
How do *YOU* tackle flat foot?

. . . do you prescribe an external wedge on the shoes?

BUT the wedges soon wear away; and very often the child is made to feel self-conscious because his shoes look different from other children's.

Surely it's more logical to have a wedge *built-in* between the inner and outer sole—invisible, and completely unaffected by wear or repair of the shoe. That is how Start-rite INNERAZE shoes are made; why they are the only practical solution to this problem.

Information from Mr. W. J. Peake, James Southall & Co. Ltd., Crome Road, Norwich.



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Invisible Wedge Shoes by START-RITE

(who make the finest children's shoes of all types)

Inneraze Shoes are supplied only against medical prescription

You ***should***

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The "Cestra" Mask

FOR SURGEONS AND NURSES

Bacteriologically tested and specially designed for the prevention of droplet infection

After many bacteriological experiments this mask was designed to arrest all droplets from the mouth and nose, and so to prevent contamination during operation. The "Cestra" Mask consists of four layers of fine dental gauze. It fastens securely under the chin, has an air gap at the sides, is comfortable to wear for long periods and may be easily sterilised.

Obtainable from Chemists and Medical Stores

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Manufacturers of all kinds of Surgical Dressings

PAINFUL GUT

'Merbentyl' deals with all painful spastic conditions of the gastro-intestinal tract. It both blocks the parasympathetic nerve endings and directly relaxes smooth muscle. This dual action gives full relief *without the unpleasant side reactions (changes of heart rate, mydriasis, cycloplegia, dry mouth, etc.) normally associated with natural and synthetic anticholinergic agents.*

BLESSING OF CHEAP CYDER
From a Litho graph by Wm. Heath

* MERBENTYL Regd.

'Merbentyl' is available in tablets (each containing 10 mg. diethylaminocarbethoxybicyclohexyl hydrochloride), and as a syrup (each 5 c.c. containing 10 mg. 'Merbentyl'). Also combined with Phenobarbitone (15 mg. (gr. ¼) per tablet or 5 c.c. syrup).

Merrell

Even on the highest dosage (8 tablets per day) the basic cost to the N.H.S. is less than 7d.

Distributed in U.K. & Eire by **BIKER LABORATORIES LTD. LOUGHBOROUGH, LEICESTERSHIRE** *for the Wm. S. Merrell Co. London.*

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AGOCHOLINE

GRANULES

Mag. Sulph. B.P., Purified Meat Peptone, and Sweetened and Peppermint Flavoured Excipient

Cholagogue and cholecystokinetic properties, stimulating biliary secretion and drainage.

Indicated in:— **SUB-ACUTE AND CHRONIC CHOLECYSTITIS, CONSTIPATION OF HEPATIC ORIGIN, FAMILIAL CHOLEMIA, ATONY OF THE GALL-BLADDER.**

Doses to be taken in the morning only, before breakfast

Basic N.H.S. Price: Tin of 100 gm. Granules, 3/1, plus 11d., P.T.

BENGUE & CO. LTD.

Manufacturing Chemists:

MOUNT PLEASANT, ALPERTON, WEMBLEY, MIDDLESEX

Canned strained foods set a mother's mind at rest

As you know, some mothers are worried when you advise early mixed feeding for baby. With so many other things to do, the difficulty of obtaining and preparing a variety of fresh foods seems almost insuperable. But Heinz Strained Foods solve the mother's problem and make it easy for her to follow your advice.

Furthermore, Heinz Strained Foods are better for baby than many home-prepared foods. Heinz get their vegetables and fruits straight from farms. And the special Heinz cooking and straining equipment preserves the maximum goodness.

So with 19 really nourishing varieties to choose from, it's easy for mother to give her baby the varied diet you recommend.

For a FREE booklet giving the nutrient values of all 19 varieties of Heinz Strained Foods, please write to Dept. 7R, H. J. Heinz Company Ltd., London N.W.10.

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SOUPS · MEAT BROTHS · VEGETABLES · SWEETS · CEREAL

Foremost among the tonic restoratives

A special formulation, its delicate flavour rendering it acceptable to the most fastidious palate and representing Vitamin B_1, Liq. Extract of Malt, the Glycerophosphates of Iron, Magnesium and Potassium, and Pepsin, together with Strychnine Hydrochloride 1/200 grain in each fluid drachm. It is indicated in devitalized conditions as it improves appetite and increases mental and physical activity

Available in 4-oz.; 8 oz.; 16 oz.; 40 oz. and 80 oz. bottles

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Let your money earn maximum interest with security

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OFFERS

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4%
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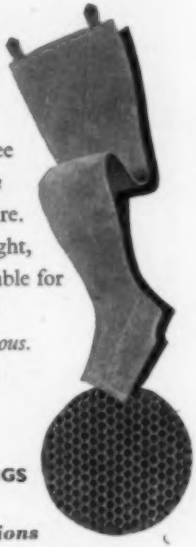
For the *Mild* Case of Varicosity . . .

. . . 'Surgylon' Hose are the obvious prescription. 'Surgylon' Elastic Net Stockings, Above-Knee or Below-Knee, are made of *nylon* open mesh net fabric of fine texture. They are seamed and provide a light, well ventilated, mild support suitable for early varices. They are eminently *comfortable, durable* and *inconspicuous.* Made to individual measurements —prompt despatch.



SURGYLON NYLON NET STOCKINGS

may be supplied against N.H.S. prescriptions

Manufactured by Everlastic Ltd. for **FASSETT & JOHNSON LTD., 86 Clerkenwell Road, London, E.C.1**

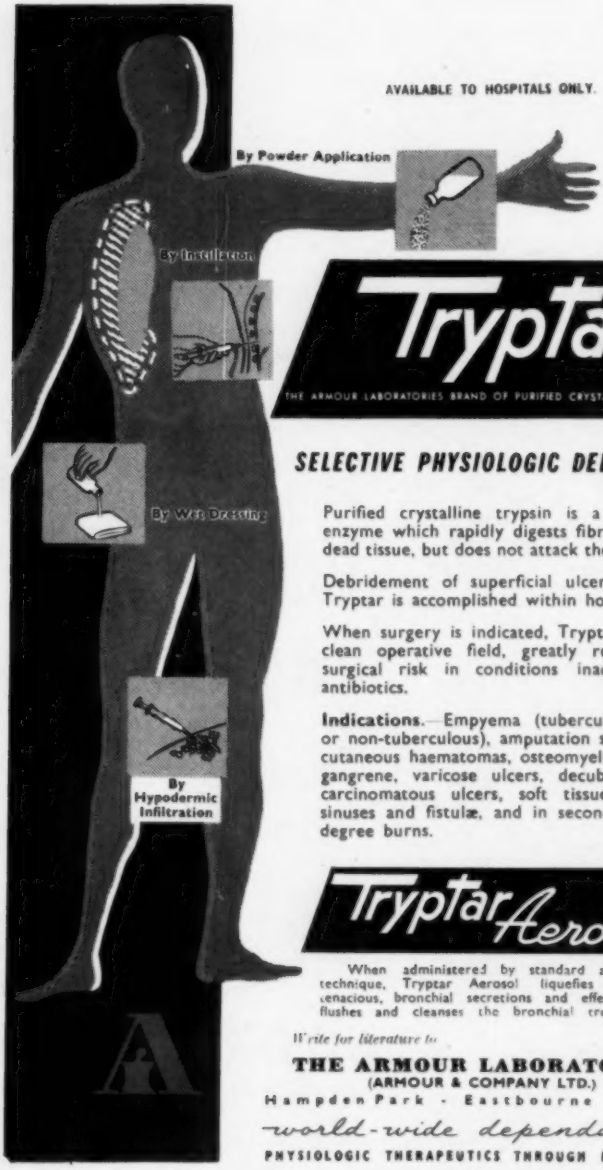
. . . the virtues of LUCOZADE

Doctor judges Lucozade from two viewpoints. He agrees with its use in the sickroom. He also finds it a most palatable drink. This palatability of Lucozade provides a long-sought answer to a long-standing problem . . . acceptability. The subtle balance between flavour, sparkle and liquid glucose content provides nourishment in a form acceptable even to the feeblest digestion; nourishment retained and assimilated. Bedside lockers bear testimony to the confidence it inspires. And many doctors have discovered for themselves the virtues of a glass of Lucozade after a hard round of work.

LUCOZADE

the sparkling glucose drink

REPLACES LOST ENERGY



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Tryptar

THE ARMOUR LABORATORIES BRAND OF PURIFIED CRYSTALLINE TRYPSIN

SELECTIVE PHYSIOLOGIC DEBRIDEMENT

Purified crystalline trypsin is a proteolytic enzyme which rapidly digests fibrin clots and dead tissue, but does not attack the living cell.

Debridement of superficial ulcerations with Tryptar is accomplished within hours.

When surgery is indicated, Tryptar creates a clean operative field, greatly reducing the surgical risk in conditions inaccessible to antibiotics.

Indications.—Empyema (tuberculous, mixed or non-tuberculous), amputation stumps, subcutaneous haematomas, osteomyelitis, diabetic gangrene, varicose ulcers, decubitus ulcers, carcinomatous ulcers, soft tissue abscesses, sinuses and fistulæ, and in second and third degree burns.

Tryptar Aerosol

When administered by standard aerosol technique, Tryptar Aerosol liquefies thick, tenacious, bronchial secretions and effectively flushes and cleanses the bronchial tree.

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THE ARMOUR LABORATORIES
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Hampden Park - Eastbourne - Sussex

world-wide dependability

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

the best things in life are not free . . .
from hyperacidity

Most patients know when their hyperacidity is caused by over indulgence in food, tobacco or drink. When the cause is not obvious, the doctor may trace gastric distress to emotional strain and nervous tension. In any case, the causes are not easy to remove, but the symptoms are—with Gelusil.
Gelusil promptly and effectively controls the excessive gastric acidity of "heartburn" and chronic indigestion. Its action is sustained, and side-effects do not occur. Gelusil leaves the patient free from constipation and "acid rebound".

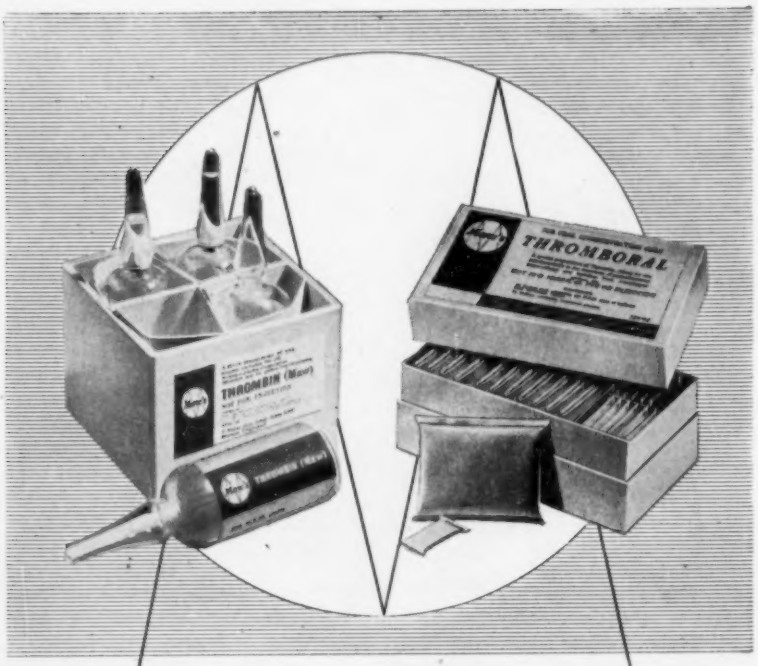
Dose: 2 tablets after meals, or whenever symptoms arise.

Formula: Each tablet contains Magnesium Trisilicate 7.5 gr. and Aluminium Hydroxide gel 4 gr.

Packing: In packs of 20 and 50 tablets. Packs of 500 available to chemists for dispensing.

GELUSIL

WILLIAM R. WARNER & CO. LTD., POWER ROAD, LONDON, W.4.



Thrombin (MAW)

For topical use in the immediate arrest of haemorrhage and for diagnostic use in obstetrics.

The haemostatic of choice in surgical or dental procedures where bleeding is from capillary vessels, or of the oozing type. Of particular value as a physiological adhesive in plastic or cosmetic surgery and for the rapid diagnosis of afibrinogenaemia in cases of excessive haemorrhage, post partum or in abortion. THROMBIN (Maw) has been proved to be of considerable value in thoracic surgical operations such as the decortication of the empyema. Presented in cartons of 2 ampoules x 200 N.I.H. Units, 6 ampoules x 50 N.I.H. and 1 ampoule x 5,000 N.I.H. Units, each with diluent.

Thromboral

A treatment for Haemorrhagic ulcers occurring in the alimentary canal.

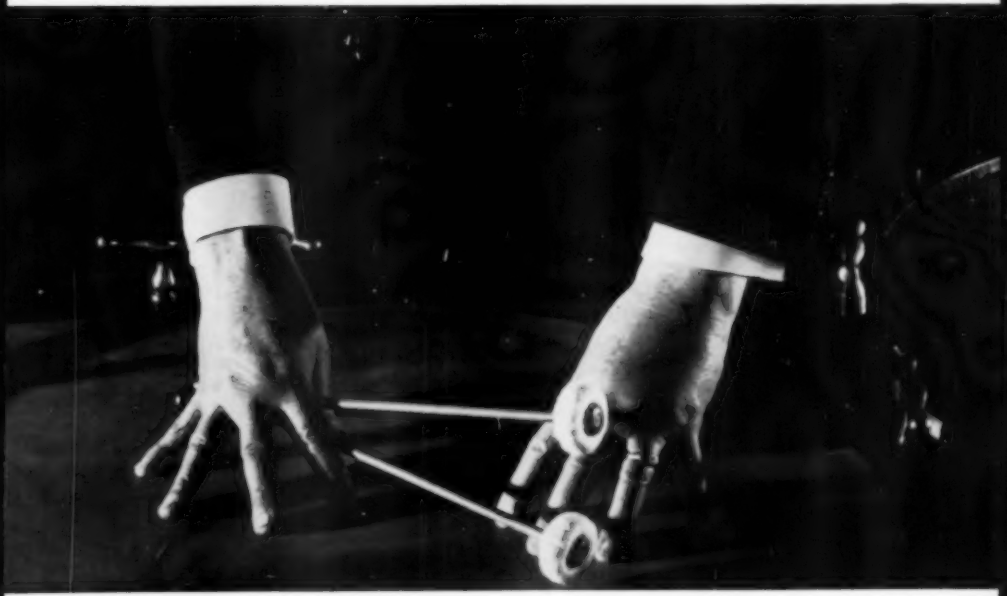
For control of haemorrhagic complications of peptic and duodenal ulcers; bleeding from ruptured oesophageal varices; denuded buccal ulcer and cases of epigastric distress exhibiting signs of internal haemorrhage, especially where the patient's age or physical condition makes surgical intervention undesirable. THROMBORAL contains active THROMBIN in substantial doses, the instantaneous effect of which is preserved by reduction of the pH of the gastric mucosa. Natural physiological coagulation occurs at the site of bleeding. THROMBORAL is presented as a complete treatment for oral administration over 24-hours.

Maw's

S. Maw Son and Sons Limited · Barnet · England

coaxing calm from climax...

To achieve calm is sometimes to cure and often to make amenable to treatment.
Calm must be coaxed from a climax which is spasm and is pain.
But not at the expense of the patient's comfort nor at the risk of his person.
The modern approach to calm in conditions of spasm is Buscopan.



BUSCOPAN to *promote the healing of gastric ulcer, Hasten cervical dilatation in labour, Facilitate radiological differentiation between a spasmodic and an organic obstruction, Overcome spastic dysmenorrhoea, Relieve pain associated with renal lithiasis or biliary colic.* **Quickly—safely—effectively.**

BUSCOPAN*

(brand of hyoscine—N—butylbromide)

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Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent, for
C. H. Boehringer Sohn, Ingelheim am Rhein,
Registered Proprietors of the trade mark.

* *Regd. Trade Mark*

IF YOU HAD TO TAKE YOUR OWN MEDICINE . . .

. . . YOU'D PRESCRIBE

Terramycin*

syrup

Quite a challenging hypothesis, Doctor, but your young patients would wish the point to be illustrated dramatically. Especially since the administration of the new TERRAMYCIN Syrup is quite the most convenient, safe and palatable way to combat a wide range of bacterial, viral, and rickettsial infections. Hydrolysing quickly in the gastro-intestinal tract, TERRAMYCIN Syrup readily yields the pure antibiotic in powerfully effective concentrations. Isn't this the way you—*mutatis mutandis*—would prefer to take your own medicine? Of course it is. And that is why you will have no difficulty in persuading pædiatric patients that TERRAMYCIN Syrup is 'very good medicine indeed'. Even the most recalcitrant youngster will be won over by its cherry flavour.

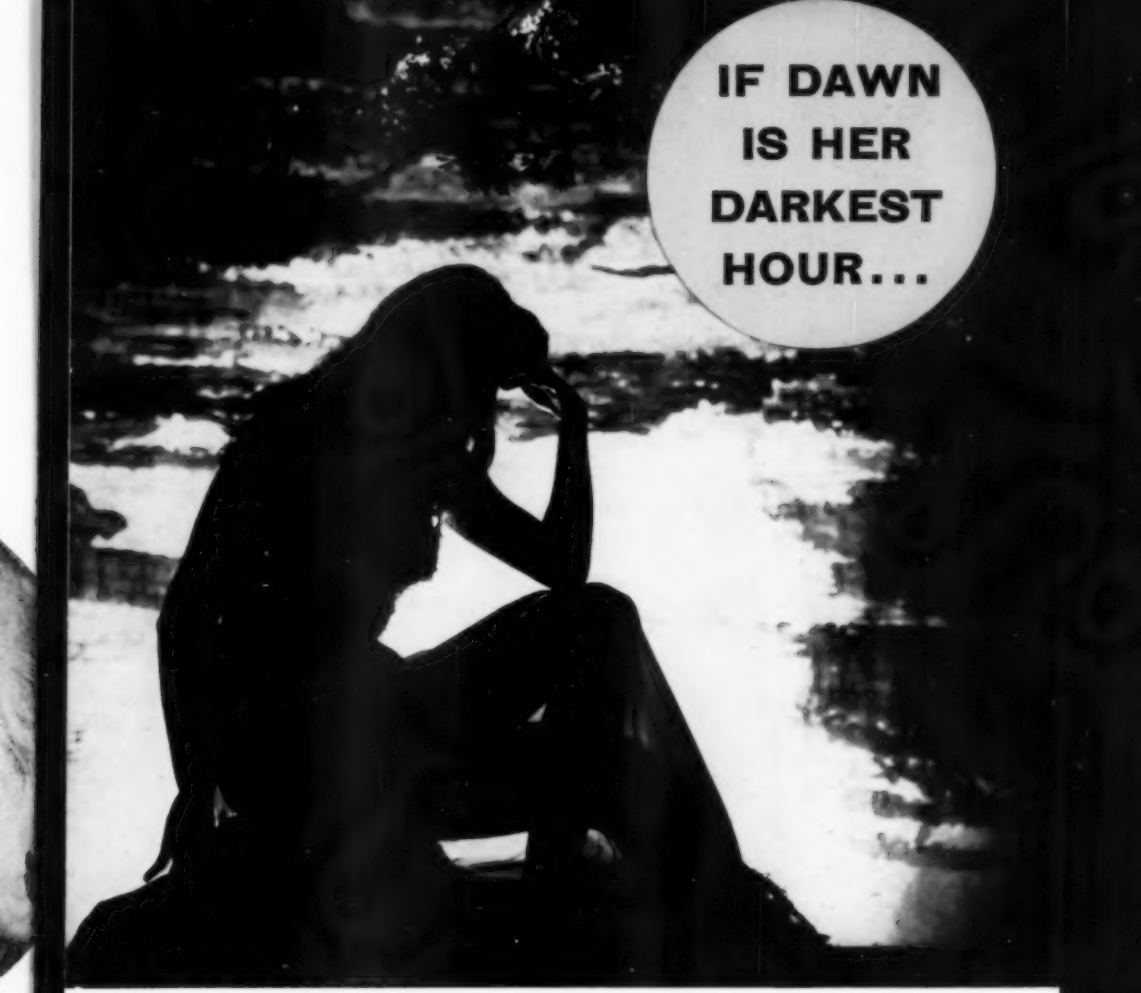
Supplied in bottles of 60 ml. Each teaspoonful (5 ml.) of which contains 125 mg. of oxytetracycline activity. Especially suitable for childen and patients unable to take tablets.

Pfizer

WORLD'S LARGEST PRODUCER OF ANTIBIOTICS

PFIZER LTD · FOLKESTONE · KENT

* *Trade Mark of Chas. Pfizer & Co., Inc.*



PRESCRIBE VIBAZINE* TABLETS

(brand of buclizine hydrochloride)

Morning sickness, so often the torment of women during the first three months of pregnancy, can now be successfully combated with VIBAZINE Tablets. VIBAZINE, brand of buclizine hydrochloride, is a powerful compound capable of giving complete relief to the majority of cases of nausea and vomiting of pregnancy. In a recent clinical trial involving cases of excessive vomiting 86 per cent. of those treated responded favourably. This response ranged from satisfactory improvement to complete relief. VIBAZINE possesses a prolonged action and is successful in small doses, without producing hypnosis; moreover, it does not exhibit the drawbacks associated with those compounds producing hypnotic effects. These combined advantages indicate VIBAZINE to be the most valuable drug yet in the control of nausea and vomiting of pregnancy.

a new compound specifically prepared for pregnancy sickness

PRESENTATION
20 × 25 mg. tablets.
100 × 25 mg. tablets.

DOSAGE
2 tablets at night.
1 tablet in the morning.

Pfizer **WORLD'S LARGEST PRODUCER OF ANTIBIOTICS**

PFIZER LTD · FOLKESTONE · KENT • *Trade Mark of Chas. Pfizer & Co., Inc*

EITHER WAY . . . THE EYES HAVE IT!

against allergy . . .

Cortril*

(brand of hydrocortisone acetate)

OPHTHALMIC OINTMENT

The remarkable anti-inflammatory, anti-allergic action of CORTRIL ophthalmic ointment makes it singularly effective in the treatment of purely external ocular conditions. Even *acute* external ocular ailments (resulting from allergic, toxic or traumatic agents) respond excellently to the topical application of CORTRIL *which gives prolonged duration of action not available in aqueous suspensions.* CORTRIL ointment is available in two concentrations —one containing 0.5 per cent. (5 mg. per G.) and the other 2.5 per cent. (25 mg. per G.) of hydrocortisone acetate. For the control of most allergic afflictions of the eye, and mild inflammatory reactions to infections and trauma, use the 0.5 per cent. ointment. Reserve the 2.5 per cent. for moderate or severe ophthalmic conditions.

against infection . . .

Terra-Cortril*

(brand of hydrocortisone acetate and oxytetracycline hydrochloride)

OPHTHALMIC SUSPENSION

Since it is desirable to prescribe both antibiotic and anti-inflammatory therapy whenever there is actual infection or its likelihood, TERRA-CORTRIL is especially suitable for afflictions of the eyelid, conjunctiva, cornea and sclera, because it combines the safe broad-spectrum effectiveness of TERRAMYCIN with the anti-inflammatory action of CORTRIL. Moreover, the gel-like vehicle of TERRA-CORTRIL promotes sustained contact of the medication with affected tissue, so that fewer applications are required. TERRA-CORTRIL Ophthalmic Suspension sterile is packed in 10 ml. amber bottles with eye-dropper.

Pfizer **WORLD'S LARGEST PRODUCER OF ANTIBIOTICS**

* *Trade Mark of Chas. Pfizer & Co., Inc.*

Pfizer Ltd.
Folkestone
Kent

16 years of clinical opinion supports the use of vaginal tampons

chafing is eliminated and there is no local irritation or internal inflammation

The chafing and itching of the vulva and thighs often associated with the use of external pads for menstrual hygiene is eliminated by changing to vaginal tampons (1). Women greatly appreciate the increased comfort and sense of freedom.

Over the past 16 years observers (1-5) have noted that tampons do not give rise to irritation of the cervix or vagina. One (5) found that cervical erosions present at the initial examination were often improved and never aggravated by the change to internal protection. No erosion, vaginitis or cervicitis is caused by this form of menstrual guard (3).

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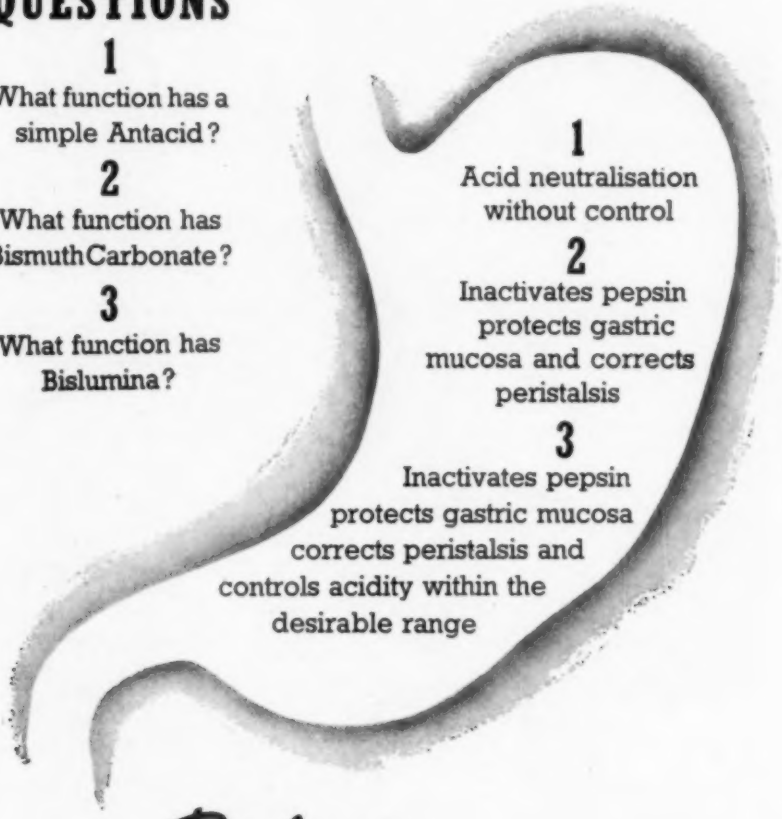
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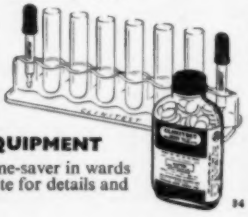

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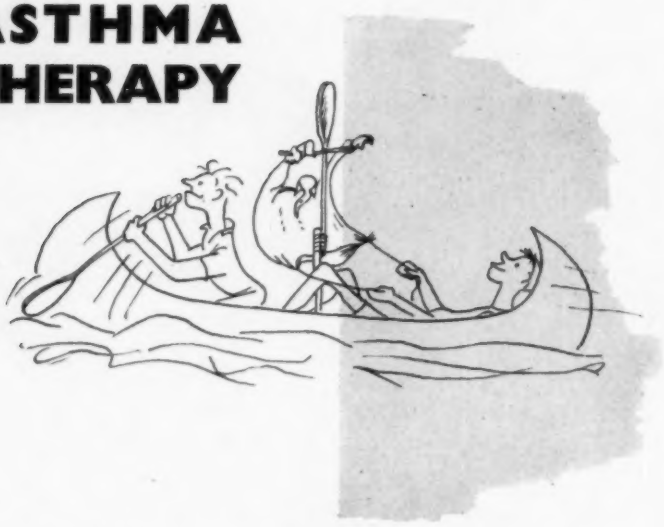

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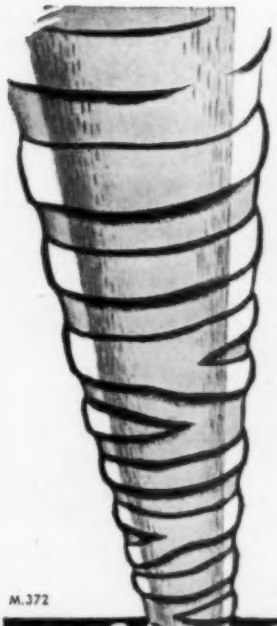

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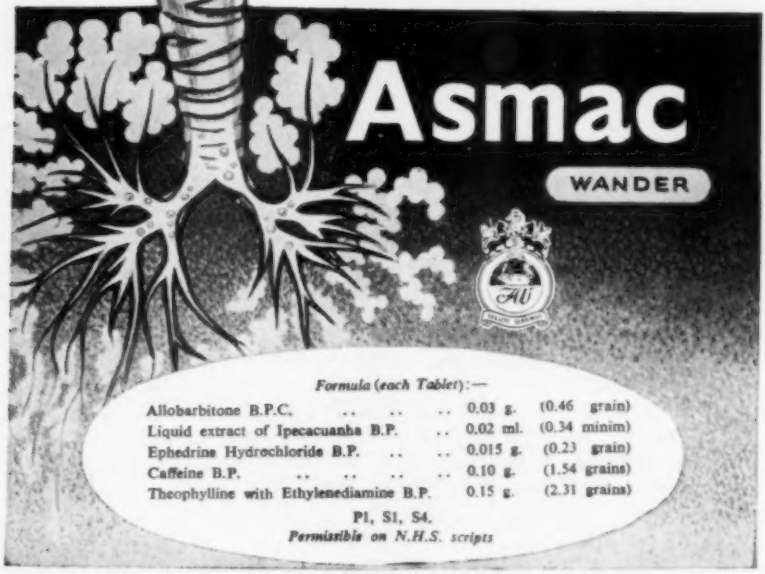

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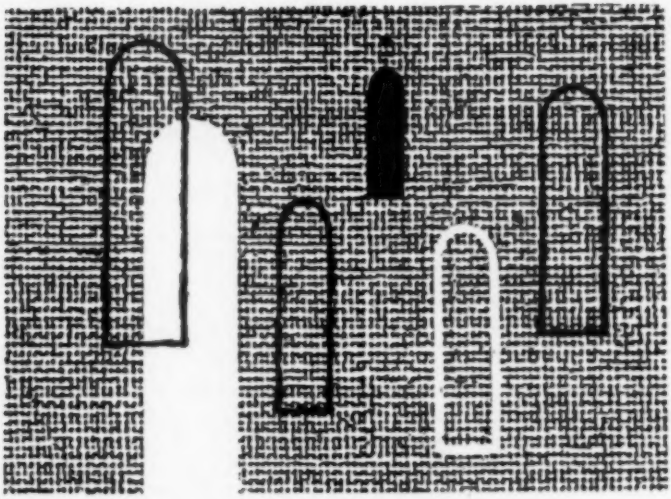

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THE PRACTITIONER

No. 1056 JUNE 1956 Volume 176

THE MONTH

The Symposium

In discussing advances in endocrinology in our special number on 'Advances in treatment' in October 1953, Dr. Raymond Greene commented that 'experimental work in the physiological laboratories of the world proceeds at such a pace that the general practitioner may count himself lucky that the practical application of new knowledge in endocrinology lags well behind'. On the other hand, it is only natural that the busy practitioner should occasionally want to have some guide as to where all this intensive work may be leading. At the same time he wants to know current views on the treatment of those well-established endocrinological disturbances which he encounters in the course of his daily work. In our symposium this month we have attempted to subserve both these functions. The management of Addison's disease and thyrotoxicosis is dealt with in detail in the first two articles, whilst the remainder of the symposium is devoted to reviews of the possible, or actual, implications of the wealth of experimental data which is pouring from the research laboratories and endocrine clinics of the world. The picture may at times be confusing, but it is clear that steady progress is being made and that the findings of the laboratory are being applied in clinical practice just as soon as it is safely possible to do so.

Value of G.P.s' Records

The wealth of information to be found in the records of general practitioners is at long last receiving the official attention it warrants. In 1951 the General Register Office instituted an analysis of the records of a small number of representative general practitioners. A preliminary review of the results of the first year of the investigation was published in November 1953 (see *The Practitioner*, 1953, **171**, 592). The results of the subsequent two years of the investigation have now been published as No. 9 in the General Register Office's series of 'Studies on Medical and Population Subjects' ('General Practitioners' Records'. H.M. Stationery Office, price 6*s*. 6*d*.). In all, 13 practitioners in 10 practices, and covering some 37,000 patients, took part. The results show that the general practitioner is consulted by about two-thirds of the patients on his list each year, and that half of the patients consulting him seek his assistance four or more times and are responsible for about 80 per cent. of all the calls on his services. Each patient on his list causes an average of 3.7 consultations a year, with men, aged 15 to 44, calling for fewest consultations (2.6 each) and women over 65 calling for most attention (5.7 consultations each). Perhaps the most inter-

esting of all is the finding that 5 per cent. of consultations were given for reasons other than sickness: e.g., routine maternity examination, general medical examination, and advice on social and domestic matters.

Interesting though these findings undoubtedly are, the primary value of this report and its predecessor is the evidence they contain of the great contribution which general practitioners' records can make to the study of clinical medicine. A larger inquiry, covering nearly half-a-million patients, is now being undertaken jointly by the College of General Practitioners and the General Register Office. Some 170 practitioners are participating in this inquiry. The results of this more representative investigation will be awaited with much interest.

A Dietetic Classic

In 1900, there appeared the first edition of Robert Hutchison's 'Food and the principles of dietetics'. This was based upon a series of lectures on dietetics which the young assistant physician to the London Hospital had instituted for the students of 'The London'. Fifty-six years later there appears the eleventh edition of this classic ('Hutchison's food and the principles of dietetics'. Revised by V. H. Mottram, M.A., and George Graham, M.D., F.R.C.P. Edward Arnold (Publishers) Ltd., price 40*s*.), and the passage of time is emphasized by the announcement that this is the last edition to be revised by Professor Mottram and Dr. Graham, neither of whom had yet entered upon their undergraduate career when the first edition appeared.

It is a striking tribute to the skill and initiative of the founder of this institution—for institution it has become in British medicine—and to the wisdom of the retiring revisers, that it is as essential a book for the practitioner of today as it was for his predecessors at the turn of the century. Age cannot wither nor custom stale its infinite variety. From the opening chapter on 'The history of dietetics', which was originally published in the January 1934 issue of *The Practitioner*, to the concluding chapter on 'artificial feeding', the book is crammed full of sagacious advice on a subject which in these latter years has tended to become the happy hunting ground of the quack and the laboratory research worker. No other book that we know of in the English language so effectively distils the dietetic wisdom of the day and interprets it in language which all can understand. Theory is not ignored, but the emphasis is all upon practice. It has had many imitators but none can match it in style, discernment and clinical sagacity.

The Train Test

A fascinating method of assessing the psychological make-up of children is described by A. Breton and P. Maurin (*Sem. Hôp. Paris*, 1956, **32**, 787). This 'train test', as it is called, is based upon the choice of seat which the child makes in a model train. The train is made up of an engine, a yellow coach with two seats, a red coach with two seats, a pullman coach with one seat, and a single-seater derelict coach which is as ugly and repellent as it can be

made. Eight children are lined up alongside this train and, at a given signal, are told to take a seat. The reaction of the children to the competition for seats—for there is always one child left without one—is studied, as well as their choice of preference. From these observations the potentialities of the children are deduced. In coming to a decision the findings in this test are correlated with the report from the child's teacher.

On the basis of this test the children can be divided into various categories. Thus, the child who chooses the seat in the engine is efficient and well adapted for the struggle of life: he belongs to the race of overlords. The child who selects the red or yellow coach will never present any problems—he has the outstanding quality of social adaptation and integration. The child who selects the pullman coach is intelligent but of a schizoid type, over-exemplary in his outward behaviour and always threatening to withdraw into his 'ivory tower'. The child who selects the derelict coach has a definite inferiority complex, and usually comes from an unsatisfactory home. Finally, there is the child who does not obtain a seat in the train. He may belong to one of two types. If he has tried and failed to obtain a seat, but shows no sign of emotional upset at being left out, he is an oligophrenic. The second type is the child who either does not try to find a place or, having tried and failed, bursts into tears or shows resentment. The former is a hyposthenic who cannot face up to the hard facts of life. The latter is the hypersthenic aggressive type who reacts violently to any frustration. This report, based upon the findings in over a thousand children, should prove of outstanding interest to all concerned with child welfare.

Arctic Epidemiology

To those of us brought up on 'Ungava' and the romance of the search for the North West Passage it is difficult to realize that the Arctic is now one of the focal points in world politics. Only 60 miles separate Alaska from Soviet Russia, and the shortest distance between the industrial centres of the United States and Soviet Russia lies across the ice floes of the Polar Sea. The population has risen in proportion to this enhanced strategical importance. In Alaska, for instance, the population has increased from 54,441 in 1920 to 205,000 in 1953, whilst the population of Soviet Russia north of 60° N. latitude has risen from 1,869,095 in 1926 to 4,210,000 in 1947. The development of the area has brought many public health problems in its train, which are ably reviewed by Joan G. Babbott and her colleagues of the Harvard School of Epidemiology (*Amer. J. med. Sci.*, 1956, **231**, 338).

Although the Arctic has no unique illnesses, the over-all picture is very different from that in more temperate and highly developed countries. Tuberculosis is the main epidemic disease. In 1953, in Alaska the mortality rate for tuberculosis in the native population was 300.3 per 100,000 population, compared with 3.6 in the white population and 12.5 in the United States. Measles still takes a heavy toll, and details are given of an outbreak in southern Greenland, in 1951, in which 4,221 of the 4,320 inhabitants

in the affected area were struck down, with 77 deaths. Heart disease affects the native population much less than the white population. Thus, in 1953, in Alaska there were 61.1 deaths per 100,000 population from heart disease in the native population, compared with 137 among the white population. The perpetually frozen state of the subsoil is a nightmare to the sanitarian. Drilling of wells is prohibitively expensive, and for all practical purposes available water is limited to melted ice or snow in the winter and surface ponds in the summer. The disposal of sanitary waste is an equally difficult problem in the long winter. In many Alaskan coastal villages, during the winter such waste is collected in empty oil-drums. As spring approaches these are placed on the sea ice, to be carried away when the annual thaw comes. In spite of all these hazards, however, the view is expressed that 'Arctic living need not be unduly hazardous or even arduous for any group, regardless of genetic or environmental background'.

Chewing the Cud

'THE value of mastication in helping to promote digestion of food has never been proved'. With this challenging statement, John H. Farrell (*British dent. J.*, 1956, **100**, 149) introduces an account of an investigation which supplies the missing evidence. By a simple, yet ingenious, method, in 10 healthy subjects he has investigated the effect of mastication on the digestibility of 29 commonly eaten foods. His method, in brief, was to sew weighed portions of masticated and unmasticated foods into separate cotton mesh bags, and then swallow them. The bags were recovered from the fæces and any food residues that they contained were examined and weighed.

Of the foods tested, 18 left large undigested residues in the fæces if they were not chewed. These included pork, bacon, beef, mutton, lamb, roast chicken, fried and boiled potatoes, and boiled peas and carrots. The other 11 foods, which included fried and boiled cod, fried kippers, hard-boiled eggs, boiled rice, white and wholemeal bread and cheddar cheese, were found to be digested easily, whether chewed or not. Of equal interest are the findings based upon the effect of varying efficiencies of mastication. These showed that the degree of mastication necessary for maximum absorption of the least digestible foods was slight and attainable by persons with dentitions that would normally be termed inadequate. Thus, in one individual with partial dentures, the removal of these, though accompanied by considerable decline in masticatory efficiency, had practically no effect upon the subject's ability to digest the food he was given. In other words, it would appear as if 'very little chewing is required for maximum digestion, and that a person having a masticatory efficiency as low as 23 per cent. may be expected to be able to masticate sufficiently well to digest any of the foods tested in this investigation'. These findings may be more popular in the nursery than in the parental dining room, but they would appear to explain the immunity from matutinal indigestion of the modern commuter with his allowance of five minutes for breakfast.

THE TREATMENT OF ADDISON'S DISEASE

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THE history of the treatment of Addison's disease is one of despair which is now giving place to hope and to confidence as increasingly satisfactory methods of control are developed.

DEVELOPMENTS IN TREATMENT

Deoxycortone acetate.—The synthesis of deoxycortone acetate made possible the effective treatment of most patients with Addison's disease. It has a chemical structure similar to the steroid hormones of the adrenal cortex. It has a marked effect on mineral metabolism, with salt-retaining properties which resemble, but are much weaker than, those of *aldosterone*, a naturally occurring and comparatively recently isolated cortical hormone.

In Addison's disease mineral metabolism is disordered and there is an excessive loss of sodium in the urine (natriuresis) and, with it, water. Potassium is retained, and the level in the blood rises (hyperkalæmia). The action of deoxycortone acetate is to reduce the excessive loss of sodium in the urine and, by increasing the excretion of potassium, to diminish the raised potassium content in the blood. It raises the blood pressure but, as it has no effect on sugar metabolism, it does not combat the tendency to hypoglycæmia which characterizes Addison's disease. It is relatively ineffective in an Addisonian crisis, and before cortisone was available the addition of adrenal cortical extract was required when a crisis was present or threatened.

Deoxycortone acetate is used in combination with sodium chloride, and, as the dosage of the latter can be easily adjusted, a flexible control is often achieved. Many people feel so well on this combination that they are satisfied that they are once again in normal health. The advent of cortisone, however, has so improved the treatment of Addison's disease that those who were previously without it admit that they had in fact forgotten what it was like to feel really well.

Cortisone and hydrocortisone are glucocorticoids of the adrenal cortex and have a marked effect on carbohydrate metabolism. They increase glycogen deposition in the liver and assist in the conversion of protein into sugar—gluconeogenesis. They thus tend to combat the hypoglycæmia of Addison's disease. They also have an effect on mineral metabolism similar to, but much weaker than, that of deoxycortone acetate, and lead to some decrease in excretion of salt and water and increase in urinary loss of potassium. They produce a fall in the circulating eosinophils and lymphocytes and,

at any rate in animals, protect against various forms of stress, such as trauma, cold and hypersensitivity reactions. Unlike other forms of treatment, cortisone and hydrocortisone lead to reduction in the pigmentation of the skin in Addison's disease, a result that is sometimes very striking indeed. They improve the condition of a patient with chronic adrenal cortical failure, whether the deficiency is due to simple atrophy or tuberculosis of the adrenal cortex as in Addison's disease, or follows subtotal or total adrenalectomy.

MODERN MANAGEMENT

Cortisone can be given efficiently and conveniently by mouth, and this is the usual route of administration. It can also be given intravenously or intramuscularly if necessary. The exact dose will have to be determined for each patient, but in most instances will be within the physiological range, i.e. between 12.5 and 50 mg. a day. These amounts are comparable to those required by patients following bilateral adrenalectomy for the relief of malignant hypertension or carcinomatosis from primary growth in the breast or prostate, and are in sharp contradistinction to the totally unphysiological amounts which are required for the control of such conditions as disseminated lupus erythematosus or polyarteritis nodosa. The individual dose is determined by observing the effect of 12.5 mg. of cortisone, three times a day, and raising or lowering it according to the response of the blood pressure, the presence or absence of fluid retention as evidenced by œdema, and the level of the serum electrolytes.

Salt, in enteric-coated tablets or capsules, is given in addition to cortisone. The dose will again depend upon the blood-pressure response and the appearance of œdema, but the amount of salt required is usually from 1 to 5 g. daily.

Deoxycortone acetate.—In some patients it will be felt that deoxycortone acetate is also required. It can be given in several ways, but subcutaneous implantation of two or three 100-mg. pellets every six to nine months, or intramuscular injections of 50 to 75 mg. of deoxycortone trimethylacetate given every three to four weeks, are the most convenient compatible with efficiency and economy. The dose of the implant or the deoxycortone trimethylacetate can be determined by 'stabilizing' the patient with intramuscular deoxycortone acetate in oil, and by then giving 25 mg. (1 ml.) of deoxycortone trimethylacetate, or implanting 80 to 100 mg. for each 1 mg. of deoxycortone acetate in oil.

INITIAL CONTROL

The current treatment of a patient with mild or moderate Addison's disease is therefore 12.5 mg. of cortisone, twice or thrice a day, with 1 g. of salt, three times a day. This will lead to reasonable control in most instances. Those patients more severely affected will require the addition of deoxycortone acetate given as deoxycortone trimethylacetate, 50 to 75 mg. (2 to

3 ml.) every fourth week, or by implantation of tablets containing 100 to 300 mg. of deoxycortone acetate every six to nine months.

FURTHER CARE

Once satisfactory control has been achieved little variation in dosage will be required, but patients must be told to give themselves an extra 25 to 50 mg. of cortisone a day if they get even a mild infection, such as a common cold, or are faced with a minor surgical procedure. They must also learn that they should take a total of 100 mg. in the day if they are feeling excessively tired, are getting cramps (due to sodium loss) or are vomiting, since by so doing they may prevent the onset of a crisis. Once the emergency is over the dose must be reduced gradually by withdrawing half a tablet (12.5 mg.) on alternate days until the initial dosage is reached.

Patients should be instructed to consult their doctors when they have any unusual or unexplained symptoms. The practitioner should take the blood pressure and, if the systolic pressure is under 110 mm. Hg or he is in any doubt about the nature of the patient's condition, he will be well advised to arrange for the serum sodium and potassium to be estimated. If the serum sodium is under 130 mEq./l. (300 mg. per cent.), and the serum potassium is 5 mEq./l. (20 mg. per cent.) or higher, the dosage of cortisone should be increased, at any rate temporarily. The practitioner must always bear in mind that, whilst patients with chronic adrenal insufficiency are particularly sensitive to cold, trauma, infection and various stresses, and thus should immediately be given treatment appropriate to such states, they may also be abnormally sensitive to various drugs in common use, such as barbiturates, bromides, opiates and other analgesics. In addition, they are very sensitive to the effects of insulin or thyroid.

THE TREATMENT OF A CRISIS

There is always the threat of the development of an Addisonian crisis, but if the foregoing precautions are observed and the dosage of cortisone increased during periods of stress, this should become increasingly rare. Nevertheless, although the condition should be largely preventable, incidents will occur, and some patients will present for the first time in crisis.

Immediately the condition is suspected steps should be taken to combat it, while at the same time efforts are made to establish the diagnosis firmly by electrolyte estimations. If the patient can retain cortisone by mouth, 200 to 300 mg. should be given in the twenty-four hours, but if vomiting is present parenteral injections should be given. Either cortisone acetate (200 mg. intramuscularly) or, if the patient is collapsed, hydrocortisone (100 mg. intravenously) can be given as a single injection. When the intravenous route is used it is preferable to add the hydrocortisone to a glucose saline drip infusion, and to run it in at the rate of 25 mg. an hour for three hours, and then at 10 mg. an hour until the patient can take cortisone by mouth. Careful control by repeated electrolyte estimations is required to avoid

excessive sodium retention or potassium loss, with the consequent risk of precipitating cardiac failure.

PULMONARY TUBERCULOSIS AND ADDISON'S DISEASE

Early on in the clinical studies of cortisone and the adrenocorticotrophic hormone (corticotrophin), it was found that following their use patients with pulmonary tuberculosis might sometimes show some improvement in their symptoms, but the sputum remained positive and the radiological appearances actually progressed. This naturally led to caution in giving these substances to patients with active or inactive tuberculosis anywhere in the body, and particularly to patients with Addison's disease whose condition is often due to tuberculosis of the adrenal cortex, with or without pulmonary lesions in addition. When, however, it was found that only small, physiological doses of cortisone were required for the control of Addison's disease it was felt that these were unlikely to have any adverse effect on an existing tuberculous lesion.

There are various reports (Browne *et al.*, 1954) in support of this view, which is now generally held (Bishop, 1955).

Browne treated five cases of Addison's disease and active pulmonary tuberculosis and, in spite of the continued use of cortisone, all the patients made a good response to streptomycin and isoniazid. Their clinical condition and radiological appearances improved, and the sputum became free from acid-fast bacilli. These patients were maintained on cortisone and salt for from 1 to 3½ years after the anti-tuberculous drugs were stopped, and there was no relapse of the pulmonary lesions. One patient was treated with cortisone for Addison's disease for two years without anti-tuberculous drugs, owing to his refusal to take them. In spite of the presence of a positive sputum, there was no change in the radiological appearance during this time.

It is therefore possible for a patient with active pulmonary tuberculosis to respond to anti-tuberculous drugs, for no spread to take place in an untreated active pulmonary lesion, and for inactive lesions to remain quiescent, while taking small doses of cortisone (under 50 mg. a day) for the treatment of Addison's disease. It must be remembered, however, that patients with Addison's disease not infrequently develop active pulmonary lesions during the course of their disease, irrespective of cortisone administration, and a routine x-ray of the chest should be taken at least every six months, and more frequently if there is any suspicion of activity. It is also worth while having periodic x-rays of the adrenal area, to establish whether or not calcification is developing, as its presence is good evidence that the condition underlying the Addison's disease is tuberculous.

THE NEWER STEROID HORMONES

The newer steroid hormones (*9-alpha-fluoro- and chloro-hydrocortisone*) have been successfully employed in the control of patients with Addison's disease (Goldfien *et al.*, 1955). Both have effects upon mineral and sugar metabolism in a manner similar to, but much more powerful than, that of hydrocortisone, and, of the two, 9-*alpha*-fluoro-hydrocortisone is the more potent.

Aldosterone has powerful salt-retaining properties and has been shown to control Addison's disease (Mach *et al.*, 1954; Prunty *et al.*, 1954). It is more active when given by intramuscular injection than by mouth (Hetzel *et al.*, 1956), but has some activity when given orally to a patient with Addison's disease (Kekwick and Pawan, 1954). Aldosterone acts much more strongly on mineral than on carbohydrate metabolism, and work in both animals and, recently, in man (Prunty *et al.*, 1955) suggests that the glucocorticoid effect is considerably less powerful than that of cortisone.

None of these hormones is as yet available for general use in the treatment of Addison's disease, but their clinical trials indicate that further steroid substances may become available for the treatment of this condition in the future.

SUMMARY

The treatment of Addison's disease has made rapid progress since the development of a synthetic mineralocorticoid (deoxycortone acetate) and the recent advent of glucocorticoids (cortisone and hydrocortisone) into clinical practice.

Cortisone is now available for general use, and practitioners can now supervise the treatment of their own patients with Addison's disease more closely than in the past.

The treatment of patients with Addison's disease of an average or moderate degree of severity will involve the use of 12.5 mg. of cortisone twice or thrice in the day, with the addition of 1 g. of salt three times a day.

When the condition is severe, deoxycortone acetate will be required in addition, and can be conveniently given as deoxycortone trimethylacetate, 50 to 75 mg. (2 to 3 ml.) every fourth week, or by implantation of tablets containing 100 to 300 mg., every six to nine months.

If the patient is exposed to an infection or unwonted stress, the onset of a crisis should be anticipated by increasing the dosage of cortisone by 25 to 50 mg. a day. Crises should be largely avoidable, but when they occur they are best treated by hydrocortisone (100 mg.) added to an intravenous drip at the rate of 25 mg. an hour for the first three hours.

The increased use of total or subtotal adrenalectomy for various conditions makes it important that the practitioner should understand the principles underlying the treatment of chronic adrenal insufficiency and the details of its execution. These are discussed in this article.

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THE TREATMENT OF THYROTOXICOSIS

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Thyrotoxicosis is still numbered among the diseases whose causes remain obscure. So long as the origin of the stimulus which provokes thyroid overactivity is unknown, treatment has to be directed against the thyroid gland. Hence it is necessarily empirical in that the final pathway through which symptoms are produced is cut and the underlying cause remains untouched. Although this is scientifically unsatisfactory, the various means of treating thyrotoxicosis are remarkably successful.

Thus the overactive thyroid can be largely removed by surgery, or the excessive production of thyroid hormone can be blocked by antithyroid drugs, or the activity of the gland epithelium can be reduced by irradiation from selectively absorbed radioiodine. But no one of these alternative methods can be considered as a treatment of choice for all cases of thyrotoxicosis. Each has its special virtues and limitations, and a method which is indicated in one case may be quite unsuitable for another. This is because there are so many variables to be taken into account. Thus different types of thyrotoxicosis may be associated with various inherent or unrelated complications which demand special attention, whilst the wishes of the patient and the availability of facilities for treatment also require consideration.

TYPES OF THYROTOXICOSIS

Broadly speaking, thyrotoxicosis embodies three main components—thyrotoxic, mechanical and cardiac—which vary in importance in any individual case. The thyrotoxic component includes all the manifestations of thyroid overactivity, the mechanical component consists of pressure effects exerted by the bulk of the goitre upon the trachea or œsophagus, and the cardiac component comprises auricular fibrillation and congestive heart failure.

Cases of thyrotoxicosis may be subdivided into primary and secondary types. This distinction can be made in almost all cases and it will be seen that the three components of thyrotoxicosis characteristically vary in prominence in each type.

Primary thyrotoxicosis, or exophthalmic goitre, usually affects young women whose thyroid glands are believed to have been previously normal. The clinical picture is almost wholly one of the thyrotoxic component. The goitre is smooth, diffusely enlarged, symmetrical and seldom large; pressure effects upon the trachea or œsophagus are exceptional, hence there is no mechanical component. In the absence of pre-existent rheumatic or other

heart disease the cardiac component, as manifested by thyrotoxic auricular fibrillation and congestive heart failure, is very rare.

Secondary thyrotoxicosis, or toxic nodular goitre, on the other hand, affects middle-aged or elderly women who have often possessed a previously simple goitre for many years. With the passage of time the goitre has slowly enlarged, becoming nodular and asymmetrical. Pressure upon, or deviation of, the trachea and œsophagus is common and the lower border of the goitre may have descended into the thoracic inlet. The mechanical component is thus often a marked feature. The cardiac component is also common and shown as auricular fibrillation or congestive heart failure, but the thyrotoxic component is, as a rule, less evident than in primary cases.

SURGICAL TREATMENT

Without any question, subtotal thyroidectomy is the quickest and surest means of dealing with most cases of thyrotoxicosis. But speed is not always essential, and in patients who do not mind undergoing some suitable but more time-consuming alternative treatment there is no need to advise surgery.

In skilled hands and with the best ancillary facilities thyroidectomy carries a mortality of less than one per cent. Results are good, relapses are uncommon and a return to normal life may be anticipated within three months. The standard operation for all types of goitre is a subtotal thyroidectomy. Experience has shown that partial operations on toxic nodular goitres, such as hemithyroidectomy or dissection-enucleation of prominent nodules, are unsatisfactory because more nodules inevitably form in the residue.

Postoperative complications such as transient tetany or some degree of hypothyroidism are readily dealt with. If auricular fibrillation has not given place to regular rhythm by the fourteenth postoperative day—which is unusual—it can almost invariably be abolished by the use of quinidine.

Preoperative preparation is of great importance. Lugol's iodine, 10 minims (0.6 ml.) three times daily for ten to fourteen days, remains the simplest and best method. It is essential for thyroidectomy to be performed when the patient has attained maximum improvement; to delay until the transient iodine remission is wearing off is to invite a postoperative crisis which may be disastrous. The best response to Lugol's iodine is obtained the first time it is given; hence it is important to reserve iodine medication as a preoperative measure. In the ordinary way there is no need to use an antithyroid drug such as methylthiouracil for preoperative preparation. It takes longer—usually about six weeks—and in any case Lugol's iodine is given for the last fortnight before operation to restore colloid to the gland and to reduce its vascularity. If, however, for any special reason it is desirable to control thyrotoxicosis and to delay operation for weeks or months, then an antithyroid drug must be given. This may well happen if a patient has pressing domestic or business commitments which prevent early thyroidectomy.

ANTITHYROID DRUGS

Methyl- and propyl-thiouracil and carbimazole are in common use. They act by blocking the formation of hormone within the thyroid gland. There is thus a time-lag of about two weeks while preformed hormone is used up before their action becomes manifest.

The theoretical rationale of this form of treatment is sound and the drugs control the thyrotoxicosis and produce a remission in at least 90 per cent. of cases, but there are several practical disadvantages which have made the treatment disappointing.

Toxic reactions.—These are admittedly uncommon and with present-day doses are due to unpredictable sensitivity of the patient, but they are always possible. Leucopenia or actual agranulocytosis is the most serious toxic effect, but drug rashes, fever, sore throat and malaise may also arise. Their incidence with the thiouracil drugs is of the order of 2 per cent. and it is said to be less than this with carbimazole. Patients should invariably be given a written list of the main untoward symptoms, namely sore throat, fever, rashes and general malaise, and be told to stop the drug and report at once if any arise. In that event a white-cell count should be done and the patient be kept under close observation, preferably in hospital, until it is clear whether or not agranulocytosis is developing. There is no point in having white-cell counts performed at routine or occasional intervals during treatment because agranulocytosis may arise in a matter of hours at almost any time during administration of the drugs, although most commonly in the first month. It is sufficient to wait until any toxic symptoms actually appear, as they cannot be predicted, but then to maintain close observation on the white-cell levels. Further administration after any toxic symptoms have subsided should only be done with the greatest caution.

Dosage.—The scheme of treatment with antithyroid drugs is to establish control of thyrotoxicosis by a relatively high initial dose, and then to use reduced amounts until the minimum effective dose is reached which can be used for maintenance. This means that the patient must be seen at regular intervals for about three months while the dose is being tapered off and then every 1 or 2 months during maintenance treatment. With *methylthiouracil*, 100 mg. twice daily is given initially for three or four weeks, then 150 or 100 mg. for two to four weeks; finally 100, 50 or even 25 mg. daily as a maintenance dose. *Propylthiouracil* is more potent (but no more effective) and is given in half the above doses. *Carbimazole* is similarly given in divided daily doses of 45 to 30 mg. daily, according to the degree of severity of the case, for two to four weeks before reduction of the dose and the establishment of a maintenance dose of 10 or 15 mg. daily.

It is impossible to lay down any hard and fast levels of dosage with antithyroid drugs beyond the initial doses, for reduction and maintenance doses will depend upon the patient's response. This can be readily assessed by the pulse rate, weight and subjective improvement. It is, however, important not to render patients hypothyroid for, apart from the unpleasant

symptoms such as bloating, coldness and lethargy, the goitre may become larger. It must also be remembered that alteration in dosage is not at once followed by objective evidence of the desired aim, and if the practitioner is impatient he may find himself overdoing the correction which he seeks.

Duration of treatment and relapses.—Although the antithyroid drugs will control almost all cases of thyrotoxicosis, a decision has to be made eventually as to the duration of maintenance treatment before their withdrawal. Experience has shown that relapse after cessation of treatment is much more frequent if courses have lasted less than six months than if maintenance therapy is continued for more than a year. Even then one cannot predict what will happen, nor how soon or late a relapse may take place. The thiouracil drugs have only been in common use in this country for ten years and carbimazole for about five, so reports of long-term follow-up studies have only now become possible.

Douglas and Kennie (1952) reported on 187 cases treated by thiouracil drugs for a year or more and then followed up at intervals of from one to seven years after cessation of treatment. They found a sustained remission without relapse in 84 (45 per cent.) cases but only 50 of these had been followed up for two years or longer and only 15 for more than five years. Similarly, Goodwin *et al.* (1954) found that 55 of 94 patients treated with thiouracil drugs had relapsed after cessation of treatment, and estimated that two out of every three patients so treated will do so.

My own experience is in accord with these results, but it will be several years before comparable information will be available for carbimazole.

At present therefore one cannot offer a patient a better chance than 1 in 3 of being permanently relieved of thyrotoxicosis by thiouracil drugs. If relapse takes place a decision as to further treatment has to be made. My experience is that patients who relapse after 12 to 15 months' treatment by methylthiouracil almost invariably do so again after a second course. The patients' confidence in the drug is justifiably shaken and they do not relish the idea of another prolonged course of treatment with the same uncertainty as to outcome. It is therefore wiser to advise alternative treatment unless the patient prefers to accept another gamble.

RADIOIODINE THERAPY

In theory, this treatment is ideal and in the future it may well be used much more than is possible now. The overactive thyroid is avid for iodine and will take up 80 per cent. or more of the administered dose of radioiodine. This selective absorption means that the body in general receives a negligible amount of irradiation and there are few or no general effects. The isotope gives off highspeed electrons within the thyroid substance and their effect is exerted only through a distance of a few millimetres. There is therefore no risk of damage to the skin or subcutaneous tissues. Radioiodine is tasteless and can be given in one calculated dose or by several smaller ones until euthyroidism is attained. Hypothyroidism may be produced after a single dose but it is not common and can readily be corrected by thyroid extract.

Radioiodine therapy, however, can only be given at hospitals where the

special apparatus and facilities exist for handling radioactive materials and disposing of radioactive excreta. This at once limits its use to some extent at present. There is also an unknown theoretical risk of late carcinogenesis in the thyroid gland which is almost certainly negligible but which cannot be assessed with accuracy for some years. Thus, for the present, radioiodine is only given to patients over 45 years of age—unless they have carcinoma of the thyroid which is amenable to this form of treatment—and it is never given to children, young adults or pregnant women.

The results of treatment in all types of toxic goitre, as recently recorded by Blomfield *et al.* (1955) are impressive. Of 140 cases, 84 per cent. were made euthyroid, 12 per cent. were hypothyroid and 4 per cent. were still toxic at the time of review. Of particular interest was their finding that cases of toxic nodular goitre did well; the goitres became smaller and the presence of tracheal compression or retrosternal extension of the goitre were not considered to be contraindications to treatment.

Having outlined the types of thyrotoxicosis and the characteristics of the various methods of treatment, it now remains to consider combinations of the two in the clinical field. The following common types of case will be dealt with: primary thyrotoxicosis, secondary thyrotoxicosis, relapsed cases, thyrotoxicosis with unrelated heart disease, thyrotoxicosis with pregnancy.

TREATMENT OF PRIMARY THYROTOXICOSIS

As already stated, the component of thyroid overactivity fills the clinical picture. All three lines of treatment—surgery, antithyroid drugs and radioiodine—can be used and the choice of one or other often rests upon the patient's own inclinations. Surgery has the virtue of speed and an excellent prospect of complete relief. Naturally, few patients want an operation if any alternative treatment has as much to offer, but in the case of the mother of a young family, or a patient about to get married, or one whose livelihood demands a quick return to normal life, then thyroidectomy is the first choice. It may seem pedantic to emphasize the need for a diagnosis of thyrotoxicosis beyond all doubt, but there are few more disappointed and difficult patients than those whose unoffending goitres have been removed and whose symptoms remain. So long as any doubt exists, thyroidectomy should be avoided.

If, however, a patient with undoubted thyrotoxicosis refuses operation or there is no urgency for restoration of health, antithyroid drugs can be used, with, in the case of the thiouracils and also probably carbimazole as well, a 30 per cent. chance of permanent remission after cessation of treatment. But the position must be fairly explained, and the warning given that subsequent thyroidectomy may be needed. In a patient over the age of 45, radioiodine therapy can be advised provided that admission to one of the specially equipped hospitals is accepted. The chance of permanent relief is greater than that offered by antithyroid drugs and equal to that of thyroidectomy.

In children radioiodine is absolutely contraindicated and surgery is best

avoided until antithyroid drugs have been tried. Should these prove unsatisfactory, or should relapse take place after a full course, then thyroidectomy must be advised.

TREATMENT OF SECONDARY THYROTOXICOSIS

The prominence of the mechanical and cardiac components in this type of thyrotoxicosis has always been a strong indication for thyroidectomy. If a toxic nodular goitre is producing pressure effects upon structures in the neck and constitutes a cosmetic embarrassment to the patient, it is much better removed. If, however, the findings of Blomfield *et al.* (1955) gain general acceptance and it is agreed that radioiodine therapy can deal with a nodular goitre as efficiently as surgical removal, then this opinion may require revision, provided always that radioiodine therapy for toxic nodular goitre will also cure or prevent thyrotoxic cardiac complications which, at present, are strong indications for thyroidectomy. As long ago as 1937, Sir Thomas Dunhill showed that thyroidectomy secured the return of regular rhythm in 248 (81.3 per cent.) of 305 cases of thyrotoxicosis with auricular fibrillation and congestive heart failure. Until some alternative treatment can equal or exceed this degree of success, thyroidectomy must remain the treatment of choice for thyrotoxic heart disease.

In the case of patients over the age of 70 or so, who do not have pressure symptoms or cardiac complications and for whom thyroidectomy would be a severe or hazardous ordeal, it is permissible to try the effect of antithyroid drugs provided that enlargement of the goitre is not produced thereby. In such a case radioiodine therapy may also be advised if the patient is agreeable to admission to a suitable hospital.

TREATMENT IN RELAPSED CASES

These may present difficult problems and much will depend upon the type of treatment which was unsuccessful.

Relapses after surgery are more common in primary than in secondary cases but in neither are surgeons anxious to operate again. For primary cases radioiodine is preferable and usually successful; antithyroid drugs may also be used but should be the second choice. Relapse in secondary cases is often the outcome of a previous partial operation at which too large a thyroid residue has been left. If pressure symptoms or cardiac complications have arisen a subtotal thyroidectomy will be the best treatment unless by that time the patient is very old or infirm, when radioiodine may be given.

Relapses after antithyroid drugs should, in general, not be treated by a further course of the same or another drug as a second relapse is very likely. Surgery or radioiodine is the alternative and the choice may well depend more upon the age of the patient than anything else.

Relapses after radioiodine therapy are uncommon and, strictly speaking, probably do not occur if initial treatment has rendered the patient euthyroid. But there is no objection to a further dose being given.

THYROTOXICOSIS WITH UNRELATED HEART DISEASE

This problem is mainly one which arises in cases of primary thyrotoxicosis in which some congenital heart lesion or rheumatic carditis is present. The added burden of thyrotoxicosis on the heart often results in the onset of auricular fibrillation or congestive heart failure which would not have arisen so early in life from either cause alone. It is naturally of extreme importance to remove the thyrotoxic element as quickly and completely as possible in order to avoid prolonged invalidism or an early death. Treatment of the thyrotoxicosis will depend largely upon the severity of the combined condition and whether or not actual heart failure is present.

If, for instance, a patient with mitral stenosis develops thyrotoxicosis and is still in regular rhythm, or has only recently broken down into auricular fibrillation without heart failure, then thyroidectomy is the best treatment after preliminary digitalization and preoperative preparation with Lugol's iodine. But if heart failure has already taken place this must be treated first with digitalis, rest in bed, and mercurial diuretics until maximal improvement has been secured. It will then be possible to judge whether thyroidectomy can be withstood, as this is certainly the best treatment. If it cannot, then antithyroid drugs or radioiodine must be used.

There is little to choose between the ultimate results of either. Slight hypothyroidism should be aimed at and maintained indefinitely. This is important, for in cases of chronic heart failure without any thyrotoxicosis the induction of permanent hypothyroidism is often beneficial. The use of radioiodine will entail transfer to an appropriate hospital and the effect of treatment, although certain, may take longer to be manifest than after antithyroid drugs. The latter, on the other hand, can be used in the patient's home and a hypothyroid effect can probably be produced in six or eight weeks by continuing a dose of 200 mg. of methylthiouracil, 100 mg. of propylthiouracil, or 40 mg. of carbimazole, daily. A maintenance dose sufficient to maintain hypothyroidism must be continued for several years if necessary or even indefinitely; no possibility of a thyrotoxic relapse can be allowed.

THYROTOXICOSIS AND PREGNANCY

It is uncommon for women with moderate or severe degrees of thyrotoxicosis to become pregnant. In most cases the patient is either mildly thyrotoxic at the time of conception or develops thyrotoxicosis early in pregnancy. It is now exceptionally rare to have to advise termination of a pregnancy and the main desideratum of treatment is to avoid miscarriage or harm to the fœtus. Radioiodine therapy is absolutely contraindicated during either pregnancy or lactation. Thyroidectomy can safely be performed up to the sixth month of pregnancy with little risk of miscarriage and, especially if the mother has other children to care for, it is the best treatment. Antithyroid drugs may also be used but great care must be exercised to ensure that maternal hypothyroidism is not produced. This may cause the infant to be born

goitrous or in a hypothyroid state. It must be remembered that the basal metabolic rate of a pregnant woman is physiologically raised to about +25 per cent. during the last three months. Treatment should not depress it below this level and, if there is any doubt, basal metabolic readings should be obtained. Astwood (1951) advised 150 mg. of methylthiouracil daily as the maximum dose for a pregnant woman during the last three months. If thyrotoxicosis has been controlled by the 7th or 8th month I prefer to stop the drug altogether for the last month of pregnancy. Relapse is unlikely to take place before parturition, and treatment can be resumed afterwards if need be. It is also unwise to give antithyroid drugs during lactation for they are excreted in the milk and may depress the infant's thyroid function. Thus, if antithyroid drug therapy is needed after parturition, the infant should be artificially fed.

CONCLUSIONS

It is hoped that this article has brought out the essential point that there is no treatment of choice for all cases of thyrotoxicosis. Treatment has been advancing and changing for the past fifty years and will continue to do so. We may anticipate the gradual disappearance of the antithyroid drugs and an increasing use of radioiodine in the future. The antithyroid drugs are certainly effective in blocking thyroid overactivity but relapse is bound to take place after withdrawal unless, by chance, the underlying stimulus of thyrotoxicosis has ceased.

Both surgery and radioiodine are much more permanent because the elimination of thyroid tissue by their respective means prevents a response to the thyrotoxic stimulus even though it still exists. Radioiodine will be used much more when the risk of late carcinogenesis in the thyroid has been proved to be negligible. This will allow treatment of many more young patients with primary thyrotoxicosis. If radioiodine can also be proved consistently to reduce the bulk of a nodular goitre, as well as to cure or prevent thyrotoxic heart disease, then it will be used a great deal more in cases of secondary thyrotoxicosis. It is unlikely, however, that surgery will ever disappear completely from the therapeutic sphere in thyrotoxicosis because the large goitre which is producing serious pressure symptoms will always demand quick removal. We may therefore look forward to radioiodine approaching, but not quite reaching, the position of the treatment of choice for all cases of thyrotoxicosis.

This is until the cause of thyrotoxicosis is discovered, when some new treatment may sweep away our present empirical methods and deal with the disease at its source.

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EXOPHTHALMOS

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EXOPHTHALMOS of some degree is found in the majority of patients with thyrotoxicosis. In a small proportion the exophthalmos is severe, and in these cases it is important to recognize that exophthalmos is the patient's dominant clinical problem; such cases are best described as ophthalmic Graves' disease, whether or not there is an associated mild thyrotoxicosis. Any lowering of their thyroid function below the normal range can worsen their eyes. As there is no easy treatment for these eyes, the management of such a patient must be dominated by the avoidance of anything which may worsen the eyes.

TERMINOLOGY

Exophthalmos, although an unsatisfactory term in many ways, is well established by usage for describing the eye features of Graves' disease. In the milder forms, there is usually no recognizable protrusion of the bulb; and even in the severer cases, the protrusion may not be readily recognized as abnormal. Until we have clearer knowledge of the nature of the condition, however, it is useful to use this same word to describe the mild and the severe grades. To avoid emphasis on one aspect of the condition, some prefer to use the clumsy term ophthalmopathy of Graves' disease.

All the earlier descriptions of thyrotoxicosis, including those of Parry, Graves, and von Basedow, mentioned exophthalmos as a feature of some, but never all, of their cases. So we now call thyrotoxicosis with eye signs or exophthalmos, exophthalmic goitre or Graves' disease. It was Plummer, in 1913, who first separated off the sub-group of thyrotoxic patients who did not show any exophthalmos and always had a nodule in their goitre: toxic nodular goitre or, more precisely, toxic adenoma, sometimes called Plummer's disease. Exophthalmic goitre, or Graves' disease, is a generalized disease, which may be precipitated in susceptible subjects by nervous and emotional causes. As well as features due to thyrotoxicosis, the syndrome includes others not dependent upon it, notably the exophthalmos and also more nervousness than that dependent upon the thyrotoxicosis. In this condition, the goitre is diffusely hyperplastic, but may also include some nodules if there has been a long-standing non-toxic goitre (fig. 1).

Correction of the hyperthyroidism will usually improve both the exophthalmos and the nervousness of the patient with Graves' disease, particularly if they are mild; but if they are severe, any over-correction is likely to worsen them. Hence, when the exophthalmos is more than slight, it is important to supplement any treatment by the normal daily requirement of thyroid: 3 to 6 grains (0.2 to 0.4 g.) of thyroid extract per day (Fraser and

Wilkinson, 1953). The causes of exophthalmic goitre probably arise outside the thyroid, from emotional and other hypothalamic stimuli leading to pituitary thyrotrophic overactivity and so to thyrotoxicosis. Toxic nodular goitre, on the other hand, arises as a local complication of a long-standing goitre; an adenoma which has become hyperplastic and functional independently of thyrotrophic stimulation. The assay of thyrotrophin in serum is technically difficult, but surveys of such an assay on patients tend to support these hypotheses (see p. 607).

FIG. 1.—Graves' disease with eye signs in a patient with a nodular goitre.

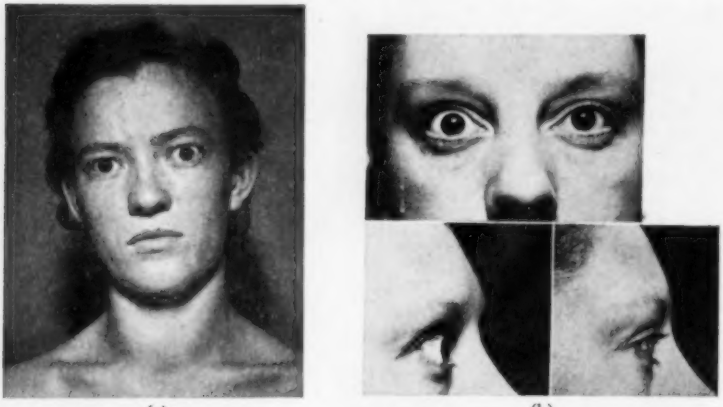
TYPES OF EXOPHTHALMOS

Many terms have been used to describe the different types of exophthalmos. All these classifications are dependent upon the recognition of the following three grades, or at least in separating the first from the two severer grades.

Mild or slight exophthalmos.—Here the only recognizable abnormalities are widening of the palpebral fissures and a tendency to upper-lid retraction. The minimal degree consists merely of a widening of the palpebral fissure or a 'stare'. It may be difficult to recognize the abnormality unless a satisfactory comparison is available: with the other eye (one is often less involved), a good previous photograph, or reliable reports by relatives of a changed appearance. There is commonly some associated upper-lid retraction: possibly only evident in a 'lid-lag' or positive von Graefe's sign, or sometimes showing even with the eyes looking horizontally forward, as a gap of white sclerotic above the iris (fig. 2). Typical Graves' disease never shows more exophthalmos than this grade; if it does, it should be called ophthalmic Graves' disease, thus signifying that the eyes are the main concern.

Severe exophthalmos.—Here there are three components, rarely all present to an equivalent degree but usually all manifest. (a) *Congestive features* are usually the earliest and most recognizable abnormalities. Watering of the eyes, especially in the morning, is at times mis-diagnosed as conjunctivitis; the conjunctivæ show congestion and chemosis (fig. 3). In the severer grades there is deep aching, especially on movement, probably also due to

congestion and tension. (b) *Muscular paresis* is at times revealed by diplopia; but before this, examination may reveal a limitation of the range of movement, especially of upward outward movement. (c) *Protrusion of the bulb*



(a) (b)

FIG. 2.—Two typical examples of slight exophthalmos:
(a) Typical Graves' disease (slight exophthalmos + thyrotoxicosis).
(b) Slight post-thyroidectomy exophthalmos.

and lids is usually not discernible until this stage, and then occurs with conjunctival congestion and muscular paresis. Although the bulb protrusion gives the name to the condition, it is the bulging of the lids which is more readily recognizable.

Malignant or progressive exophthalmos.—This grade comprises the extreme instances of the former, from which it is differentiated by the additional features of significant impairment of visual acuity and rapid advancement in the condition.

It is the prognostic significance which justifies this separation into grades. The slight grade almost always occurs with thyrotoxicosis, as part of the syndrome of Graves' disease, and when the thyrotoxicosis is corrected it can be relied upon to go; although the explanation of this clinical fact is still awaited. Only the severe grade carries the risk of passing into the malignant phase with its acute threat to the eyesight. The slight grade shares so few clinical features with the other two that it has often been regarded as a separate clinical entity. Corresponding closely with the separation of slight exophthalmos from the other grades, Mulvany (1944) has distinguished thyrotoxic from thyrotrophic exophthalmos; Plummer and Wilder (1935) distinguished exophthalmos with a high basal metabolic rate (B.M.R.) from that with a low B.M.R.; and the terms post-thyroidectomy exophthalmos and exophthalmic ophthalmoplegia (Brain, 1938) have been used to describe the exophthalmos which is clearly more than part of the picture of typical Graves' disease.

EXAMINATION OF THE EYES FOR EXOPHTHALMOS

It is not important to check the presence or absence of the various 'eye signs' to which famous names have become attached, but it is important to examine all cases suspected of thyrotoxicosis or of exophthalmos, so that any exophthalmos present may be graded into one of the three categories just described. When more than slight exophthalmos is found, the degree of the disorder must be followed carefully throughout treatment, and especially by regular checking of the visual acuity so that any tendency to pass into the malignant phase may be noted.

FIG. 3.—Ophthalmic Graves' disease with severe exophthalmos.

Slight exophthalmos or lid retraction.—The minimal easily recognizable sign is 'lid-lag' or the positive von Graefe's sign. To avoid false positives, this sign must be elicited carefully. Frightening of a nervous patient can lead to a temporary positive von Graefe's sign, especially in hysterical patients and in actors (fig. 4). The patient should be asked to follow the finger up and down several times and not too slowly; only persistent lagging of the upper lid behind the limbus should be scored as a positive von Graefe. This sign may be absent in the severe grades of exophthalmos, and indeed may be found occasionally in conditions other than Graves' disease—notably in nervous patients such as those with peptic ulcer. But in these patients the sign is usually not persistent.

FIG. 4.—Pseudo-lid-retraction in an actor's daughter (two minutes separate the photographs).

For severe exophthalmos.—Irrespective of the former signs, search should

next be made for signs of congestion—by inquiring for watering, and by examining the lateral conjunctiva (see fig. 3). The eyes should be moved through their full range, upwards, downwards, inwards and outwards; the

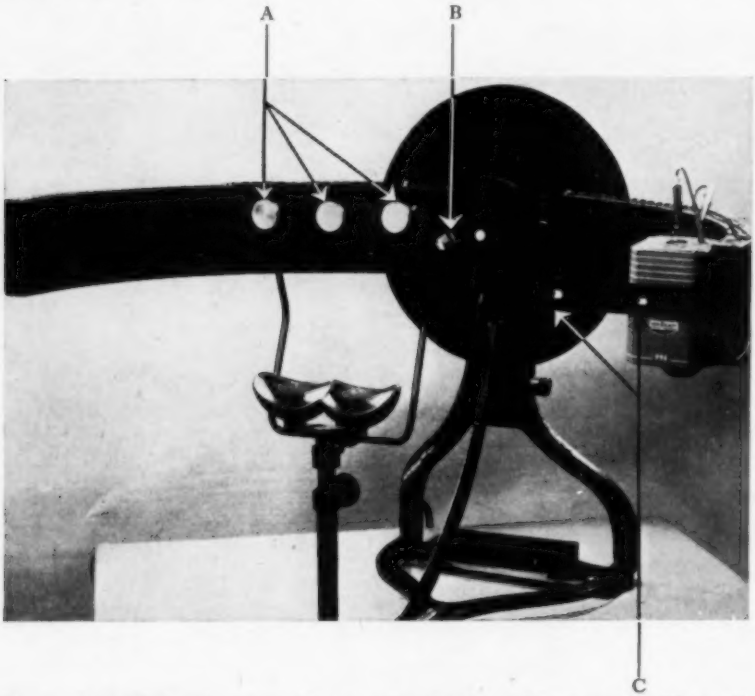


FIG. 5.—A modified perimeter used for recording the range of eye movement. The modification consists of replacement of the moving spot by a torch bulb, and the addition of a pair of forehead rests which prevent lateral movements of the head.
A: Forehead rests (adjustable height) to prevent rotation of the head.
B: Torch bulb which the patient's gaze follows (and whose reflex is from the pupil centre so long as he can follow it).
C: Sights for adjusting height of chin-rest to mid-corneal level.

patient should be asked to report any diplopia during these manœuvres but movement of less than 40 degrees in any direction is also subnormal. Finally the patient should be examined from the side with the eyes lightly closed, to see whether the lids bulge forward between the orbital margins and the bulb—the first sign of true proptosis.

For malignant exophthalmos.—Finally, especially with any of the previous signs, a quick check of visual acuity should be made. If this shows definite signs of deteriorating progressively, the malignant phase has been entered. This might depend upon corneal ulceration, bulb distortion or nerve head pressure; in such cases therefore the cornea and fundus should also be carefully examined.

THE MEASUREMENT OF EXOPHTHALMOS

Three aspects of this condition may be measured to follow its progress or response to treatment. Visual acuity, measured in any of the usual ways but most simply by Jaeger charts, comes first as the simple method which will reveal any serious threat to the eyes—the malignant phase of exophthalmos. Probably the next most useful measurement is that of the range of eye movements; which may be recorded with a slightly modified perimeter (fig. 5)—in the same fashion as Rundle and Wilson (1942) have done with a special instrument. It is usually sufficient to record the upward half of the range of movement at 45-degree steps, including a single downward movement as a check on the centring. The mean of the upward movements (vertical + the two movements upward at 45 degrees on either side) constitutes a good index of the range of movement, since upward movement is usually the most severely involved. It is also possible to measure the protrusion of the eye forward by an exophthalmometer, of which Hürtle's is the most popular; this records the number of millimetres by which the cornea projects in front of the outer bony orbital edge. As the exophthalmometer measurement normally varies from 12 to 17 millimetres, according to the patient's build, this measurement is only useful for charting progress. The protrusion or exophthalmos can also be measured by using a Copper orbitonometer (1948); in addition, this instrument measures the compressibility backwards of the eyeball along the orbit.

PATHOPHYSIOLOGY

Mechanics.—In slight exophthalmos, where lid retraction is the only recognizable abnormality, the term exophthalmos is really inappropriate, although there may be slightly more protrusion than that normal for the patient. The stare and the lid retraction are due to spasm of the levator palpebræ superioris, possibly the consequence of weakness in the superior rectus muscle. This was previously attributed to sympathetic stimulation, but Pochin (1939) has made out a strong case against this hypothesis. In the severe cases, although lid retraction may be lost, there are two other important mechanical abnormalities: an increase in the bulk of the orbital contents, and a weakening and lengthening of the extra-ocular muscles (Rundle and Pochin, 1944; Rundle, Finlay-Jones and Noad, 1953). The consequent increased retrobulbar pressure is the central feature of the disorder. These mechanical abnormalities arise in association with histological changes seen mainly in the extra-ocular muscles. They also lead to compression and kinking of the venous effluents of the orbit; thus arise the congestive phenomena so universally a sign of the severe grades of exophthalmos. Exophthalmos has been produced in animal experiments by cervical sympathetic stimulation and by other means which cause contraction of Müller's orbital muscle; but these probably do not apply to man with his differently shaped orbits (Brunton, 1949).

Histology.—No abnormality has been described in association with the

slight grade of exophthalmos, but Rundle and Pochin found an increase of fat in these orbits, and abnormalities similar to those of the severe grades may exist in a minimal degree. In the severe or malignant grades of exophthalmos, a characteristic picture is to be seen. The extraocular muscles are swollen to 3 to 8 times their normal size, and on microscopy these muscles show degenerative signs in the muscle fibre, including loss of striation and increased fat content. Between these fibres is a round-celled infiltration, particularly perivascularly, together with a progressive fibrosis. There is also some increase in the other tissues of the orbit, and some degree of œdema though most of the swelling is not due to œdema. Asboe-Hansen, Iversen, and Wichmann (1952) found an excess of muco-polysaccharides in the muscles and in the connective tissue of these orbits, but others have not confirmed this finding. A small proportion of patients with severe exophthalmos also show pretibial or localized myxœdema (Trotter and Eden, 1942) (fig. 6)—a condition never found apart from Graves' disease with exophthalmos and possibly reflecting a pathological basis similar to that of exophthalmos.

FIG. 6.—Pretibial myxœdema in a patient with thyrotoxicosis and exophthalmos similar to that shown in figure 3.

Causation.—As the causation is not yet finally clarified, I shall refer only to the main experimental findings. Exophthalmos, although closely connected with disorders which may lead to thyrotoxicosis, is clearly not due to abnormal thyroid function. It occurs as a part of Graves' disease, commonly in association with increased thyroid function, but the exophthalmos of Graves' disease may precede the thyrotoxicosis, and, with severe exophthalmos, any associated hyperthyroidism tends to be slight. Indeed, severe exophthalmos may develop or increase following thyroidectomy for Graves' disease (Naffziger, 1954), particularly if the thyrotoxicosis is overcorrected, whether by thyroidectomy, by antithyroid drugs, or by radioiodine (fig. 7).

The exophthalmos has been attributed by many to excessive secretion of thyrotrophin (T.S.H.) by the anterior pituitary.

This was first suggested from the experimental production of exophthalmos by in-

jections of T.S.H. into rabbits by Marine and Rosen (1934), and into guinea-pigs by Smelser (1937) and by Dobyns (1946, 1950). This exophthalmos is associated with a round-celled and œdematous infiltration of the loose orbital tissues and muscles. These changes closely resemble those found in human post-thyroidectomy

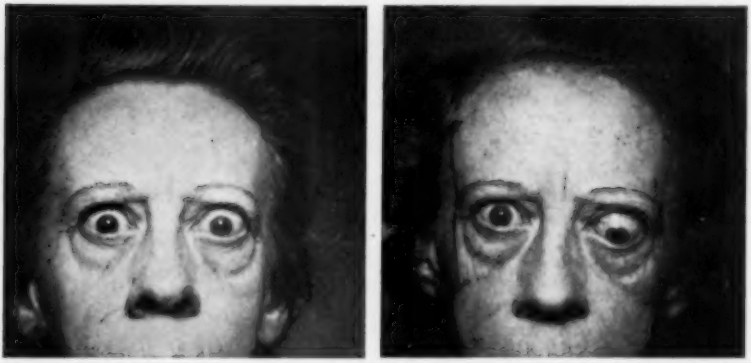


FIG. 7.—Worsening of severe exophthalmos as a result of overtreatment of the thyrotoxicosis (later remedied).

and other types of severe exophthalmos, except that in this experimental exophthalmos, œdema and fluid retention are more prominent, possibly because of the more rapid development of the condition. Dobyns showed that the changes spread beyond the orbits, involving muscular degeneration in other sites and also generalized fat mobilization. Dobyns (1946) and Dobyns and Steelman (1953) showed that experimental exophthalmos could be produced by a more highly purified anterior pituitary factor largely free of T.S.H., which he has called the 'exophthalmos producing factor' (E.P.F.), and for which he has developed a bio-assay (Dobyns and Wilson, 1954). He has postulated that exophthalmos is due to a special type of antero-pituitary overaction involving excess production of this factor, an excess of which he has found in the serum of some but not all of his cases of severe exophthalmos. This, however, has yet to be confirmed.

Unfortunately, the amount of T.S.H. circulating normally is too small for certain measurement, so that despite several surveys of the serum and urine concentration in various patients, it is not yet settled whether severe exophthalmos is always associated with increased circulating T.S.H. The most sensitive assay procedures find increased T.S.H. circulating in most but not all cases with severe exophthalmos, and decreased levels in thyrotoxicosis without associated exophthalmos (Gilliland and Strudwick, 1956). It is not yet clear whether the exceptional cases are due to faulty assays or temporary absence of the T.S.H., or whether they really represent a different condition in which antero-pituitary overactivity is not involved. Hypophysectomy has been carried out in one severe example of exophthalmos with reported cure of the condition (Albeaux-Fernet *et al.*, 1955).

It must be remembered that exophthalmos does not occur in spontaneous myxœdema in which a similar excess of the circulating T.S.H. is also demonstrable, and that the exophthalmos of Graves' disease may persist even when the Graves' disease patient develops spontaneous myxœdema

(fig. 8). Evidently severe exophthalmos may be a consequence of the increased antero-pituitary activity of Graves' disease, an increased activity which includes increased thyrotrophin production. On the other hand, the

FIG. 8.—An example of severe exophthalmos persisting in a patient with chronic Graves' disease who developed spontaneous myxœdema.
(a) Patient during phase of spontaneous myxœdema.
(b) Same patient after treatment with thyroid.

increased thyrotrophin alone without some other aspect of Graves' disease is apparently insufficient to produce exophthalmos: possibly there is some other form of increased antero-pituitary activity involved. Exophthalmos can be produced or facilitated by cortisone and testosterone (Aterman and Greenberg, 1953); but the relevance of this observation to exophthalmos in man is not yet established.

DIFFERENTIAL DIAGNOSIS

Slight exophthalmos may be seen in a number of nervous conditions, for

example in peptic ulcer. Some of these may be examples of pseudo-lid-lag, which can be recognized by the fact that it is not persistent under careful examination. Provided there are no other features of exophthalmos or

(a)

(b)

FIG. 9.—Bilateral exophthalmos due to lymphoma, which responded to deep x-ray therapy. (a) 22.1.53. Before treatment. (b) 6.2.53. After treatment with deep x-rays.

thyrotoxicosis this condition calls for no action. Severe exophthalmos always calls for an adequate diagnosis and careful follow-up until the condition is definitely subsiding. The important conditions to be considered here are orbital tumours (fig. 9), sepsis extending from the nasal sinuses (fig. 10) and cavernous sinus thrombosis (which is usually due to nasal sinusitis unless its cause is obvious).

It is never satisfactory to diagnose exophthalmos as due to Graves' disease unless both eyes are involved to some extent and there is also some evidence of increased thyroid activity, however slight. The condition is often asym-

metrical but usually the better eye shows at least a positive von Graefe's sign; unless it does so, these other orbital diseases mentioned in the preceding paragraph cannot be safely excluded without special tests. X-rays of the skull, to show the orbital foramina and walls and the nasal sinuses, may reveal such a cause. Because it is so amenable to treatment, it is particularly important not to miss sinusitis as a cause (fig. 10).

FIG. 10.—Right exophthalmos from chronic ethmoiditis.

PROGRESS OF THE CONDITION

As already noted, slight exophthalmos is usually part of the picture of typical Graves' disease, and disappears with the correction of the thyrotoxicosis. Following thyroidectomy the measurable protrusion of the bulb (with a Hürtle exophthalmometer) increases slightly but the other signs usually disappear. Ophthalmic Graves' disease, in which the exophthalmos is more marked than the thyrotoxicosis, usually has a slow spontaneous course; it generally takes three to six months to worsen to its maximum, and then one to two years to regress (Rundle and Wilson, 1944, 1945). As already noted, lowering of thyroid function below the normal range will worsen this condition (Naffziger, 1954). Rarely, even without this precipitant, the severe exophthalmos may pass into the third or malignant grade, and then it may rapidly worsen; unless arrested, it leads to corneal ulceration, papillœdema, dislocation of the eyeball and ultimately panophthalmitis. Of all the aspects of severe exophthalmos, the congestive aspect is the one which is most likely to be responsive to any form of treatment, and the longer severe exophthalmos has lasted the less likely is full or rapid regression, probably because of the fibrosis which steadily develops while the active condition is present.

THE TREATMENT OF SEVERE EXOPHTHALMOS

Simple measures.—The condition of the thyroid should be corrected, pro-

vided care is taken to avoid overtreatment. Tablets of thyroid, 3 to 6 grains (0.2 to 0.4 g.) daily, should be prescribed throughout any such treatment and for three months following its completion, whether surgery, radio-

(a) (b)

FIG. 11.—Severe post-thyroidectomy exophthalmos treated by orbital deep x-rays and cortisone. (a) Before treatment. (b) After treatment.

iodine or antithyroid drugs are being used. Although overtreatment of thyrotoxicosis may worsen the condition, restoration of hyperthyroidism to normal thyroid function often improves even the severe grades of exophthalmos as well as slight exophthalmos. Along with this correction of the thyroid status, other simple measures can help: e.g. attention to the nervous state of the patient, sleeping with the head elevated by several pillows to aid drainage, and dehydrating regimes such as a low-salt diet. When the diplopia is the main disability, glasses with one side frosted are often helpful, provided the earpieces can be moved backwards and forwards so that the eyes can be used alternately.

Special medical measures.—If the condition is still a handicap, various other measures can be tried. Administration of thyroid to the point of producing slight toxic symptoms is said to help. Deep x-rays to the anterior pituitary or to the orbit have been found helpful in some cases. The administration of cortisone (100 to 200 mg. daily for a period of two to three weeks) helps some cases, especially those with congestive features (fig. 11) (Medical Research Council, 1955). Local injections of hydrocortisone and of 'hyalase' have been tried, with limited benefit. Other hormones have been used, but probably do not help. These two groups of measures usually suffice to prevent any worsening of the condition and, over some months, often remove all the patient's disabilities. Only once have I had to resort to a Naffziger operation.

Surgical treatment.—(i) *Emergency—the Naffziger operation.*—This operation is unquestionably indicated when the patient enters the malignant phase and over a few days the eye or eyes continue to worsen. This, how-

ever, is probably the only indication for this operation. Professor Naffziger himself has performed only 40 such operations in twenty years. The cranial cavity is entered and as much as possible of the roof and lateral walls of the orbit are removed to relieve the pressure in the orbit.

(ii) *Other operations.*—Various other operations have been used, but probably have little place except for correcting the late stabilized muscle abnormalities. Tarsorrhaphy may be used to diminish the risk of corneal ulcer, but medical measures suffice in many cases. Tarsorrhaphy has also a small place in some late cases to pinch together the edges of the eyelids and so diminish the unpleasant stare. When the eye condition has become stabilized, i.e. after at least one to two years, diplopia may still remain as a major residual disability. Here the surgeon can rebalance the eye axes, and so remove the residual disability.

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HYPOPITUITARISM

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KNOWLEDGE of pituitary function in man has been greatly advanced in recent years. In the following account of hypopituitarism the aim will be to examine the syndrome in terms of the failure of individual hormones, and to indicate some of the methods now used in the diagnosis and treatment of the condition.

DEFINITION AND CAUSES

Hypopituitarism is a condition of endocrine failure due to lack of one or more secretions of the adenohypophysis or anterior lobe of the pituitary gland. Use of the term panhypopituitarism is best restricted to severe cases of the syndrome of which Simmonds' disease, as originally described, is an extreme example.

Seven hormones are now known to be secreted by the adenohypophysis. These are growth hormone, the gonadotrophins (follicle-stimulating and luteinizing hormones), lactogenic hormone, corticotrophin (ACTH), thyrotrophin (TSH), and the melanocyte-stimulating hormone (MSH). Of these, the first four, especially the gonadotrophins, seem to be more vulnerable to failure in early or incomplete lesions of the pituitary gland.

Rarely hypopituitarism is congenital. It can then be remarkably selective with loss of only one or two pituitary secretions, such as growth hormone (Hewer, 1954) or the gonadotrophins (Wilkins, 1950a). In most cases the condition is acquired from extensive destruction of the adenohypophysis by tumour, infarction, granuloma, infiltration or atrophy. In children, the most common tumours are craniopharyngiomas (Rathke's pouch rests, suprasellar cysts) and gliomas of the optic chiasma; in adults, chromophobe and eosinophil adenomas (late acromegaly) and carcinomatous metastases from bronchus or breast.

In women the most common cause of hypopituitarism is infarction of the anterior lobe following severe post-partum hæmorrhage or shock (Sheehan's syndrome). This lesion is more liable than a tumour to cause subtotal destruction of the adenohypophysis and so accounts for a large proportion of the severest cases (Sheehan and Summers, 1949). Pituitary granulomas may be syphilitic, tuberculous, or sarcoid, though their origin is often obscure. The xanthomatous infiltrations of Schüller-Christian disease may be extensive enough to interfere with anterior as well as posterior pituitary function. It has been suggested that the hypogonadism of hæmochromatosis, which is often an early symptom, may be secondary to damage to the gonadotrophin-secreting basophil cells of the adenohypophysis by iron deposition (Hubble, 1952).

In many cases the cause of pituitary failure cannot be established during life, and the possibility of a primary hypothalamic factor must sometimes be considered. To what extent pituitary function in man is under hypothalamic control is not yet known. It is clear, however, that hypogonadism and dwarfism can both result from hypothalamic lesions, as in the Laurence-Moon-Biedl syndrome and some cases of Fröhlich's syndrome. Undernutrition or prolonged debility in children can lead to dwarfism and delayed puberty, indistinguishable from hypopituitarism; and anorexia nervosa has its accompaniment of secondary or functional hypopituitarism.

CLINICAL TYPES OF HYPOPITUITARISM

Hypopituitarism evolves in its purest form after post-partum necrosis of the gland. With pituitary tumours the clinical picture is often obscured by the effects of pressure on neighbouring structures such as the optic chiasma, frontal or temporal lobes, hypothalamus or neurohypophysis. Thus, failure of vision, personality changes, fits, obesity, disturbances of sleep rhythm or diabetes insipidus may predominate, and there may be little or no evidence of hypopituitarism. The hypogonadism of Fröhlich's syndrome is more often due to hypothalamic, than to direct pituitary, involvement by a suprasellar cyst.

Prepubertal.—Most of the clinical features of hypopituitarism can now be described in terms of discrete hormonal deficiencies, although the cause of anæmia and achlorhydria is not quite clear. The clinical picture depends upon the age of onset and the severity, speed and selectivity of the pituitary failure. The childish pattern differs from the adult in that growth is retarded and puberty averted. In rare congenital cases, only one or two pituitary secretions may be lost, such as growth hormone or the gonadotrophins. In acquired lesions of childhood both these functions are affected (pituitary infantilism), and there may be varying degrees of corticotrophic and thyrotrophic failure (fig. 1). With survival into adult life growth continues, but at an extraordinarily slow and decelerating rate, and the epiphyses may never unite. Although adult in years, the facies has a characteristic pale and childish look.

Postpubertal.—When the onset is gradual and postpubertal the gonadotrophic secretions almost always fail first and many cases never pass beyond this incomplete phase of the syndrome. The symptoms are insidious and may easily be overlooked. The sexual libido declines and in the male there is a shedding of sexual hair (face, perianal, sub-umbilical, chest and limbs), feminization of the body contours, softening of the testes, atrophy of the prostate and impotence. The facies is pale and rather featureless and may become prematurely wrinkled. In post-partum cases lactation often fails, from cessation of lactogenic hormone secretion, and this is usually followed by amenorrhœa which may be abrupt or preceded by a period of progressive hypomenorrhœa. There is gradual atrophy of the uterus, ovaries, breasts, vulva and vaginal epithelium. These changes cannot be distin-

guished from those of the menopause and are therefore of diagnostic value only when they have occurred in younger women. In mild or subclinical cases of pituitary infarction lactation can occur and symptoms may be long

FIG. 1.—Hypopituitarism and left optic atrophy due to a craniopharyngioma in a girl of 11. Her height and weight were just below the one percentile limits of normal although her parents were both of normal stature. She showed signs of adrenocortical failure (pallor; B.P. 85/40 mm. Hg; fasting blood sugar, 57 mg. per cent.; electrocardiographic abnormalities (fig. 5); delayed water diuresis; very low urinary corticoid excretion). These abnormalities were fully corrected by cortisone, 12.5 to 25 mg. a day. There was no clinical evidence of thyroid failure, and the radioiodine uptake was normal.

delayed. Further pregnancy may then ensue, although with doubtful effects on the ultimate prognosis. It is also questionable whether vague symptoms of ill health should be attributed to hypopituitarism unless accompanied by amenorrhœa or scanty menses.

Adrenal and thyroid failure.—The next stage is one of insidious adrenocortical and thyroid failure, due to loss of the corticotrophic and thyrotrophic secretions. Evidence of adrenal failure often precedes that of hypothyroidism, and when the stage of myxœdema has been reached there are almost always signs of adrenal insufficiency. The adrenocortical functions which are affected are those dependent upon corticotrophin, namely, the secretion of hydrocortisone and of adrenal androgens. Aldosterone, the adrenal salt-retaining hormone, is largely independent of pituitary control and its secretion probably continues, at least in the earlier stages of pituitary-adrenal failure (Luetscher and Axelrad, 1954). Lack of hydrocortisone accounts for the Addisonian features of the syndrome, such as hypotension, postural faints, pallor, muscle weakness and mental asthenia, undue susceptibility to effects of trauma and infections, spontaneous hypo-

glycæmia, increased insulin sensitivity, and a tendency to water intoxication; it seems also to be the main factor predisposing to hypopituitary coma (Caughey and Garrod, 1954, 1955). Adrenal androgen failure contributes to the general weakness and loss of sexual and body hair.

Pituitary-adrenal failure differs from primary adrenal failure in at least two important respects: first, instead of increased pigmentation there is loss of melanin from the skin due to absence of the pituitary melanocyte-stimulating hormone (MSH) (Shizume and Lerner, 1954). Both MSH and corticotrophin are increased in Addison's disease (Shizume and Lerner, 1954; Sydnor *et al.*, 1953). Secondly, severe sodium depletion is uncommon in hypopituitarism, probably because of continued secretion of aldosterone. With advancing hypopituitarism the classical signs of myxœdema become obvious (fig. 2), and the end may be hastened by hypothermia, coma, or convulsions.

FIG. 2.—Panhypopituitarism due to post-partum pituitary necrosis. Note severe features of myxœdema.

TOTAL HYPOPHYSECTOMY

When total hypophysectomy is undertaken to alleviate intractable cancer or diabetic complications, part of the pituitary stalk is also removed. The operation is therefore followed not only by rapid failure of those endocrine functions dependent upon the adenohypophysis but also often by diabetes insipidus. As in experimental diabetes insipidus from section of the pituitary stalk, there is an early transient phase of polyuria followed by a normal (antidiuretic) interphase lasting from one to two weeks. Finally there may be a prolonged or permanent phase of diabetes insipidus which, in the absence of adrenal glucocorticoid secretion, depends for its persistence upon exogenous cortisone (Ikkos *et al.*, 1955). If cortisone is then withheld the urinary output falls to normal although the specific gravity, even after fluid deprivation, seldom exceeds 1015. The diabetes insipidus tends to recover partially after three to six months (Luft *et al.*, 1955a).

Symptoms of acute adrenocortical failure with hypotension, but without salt depletion, may occur within a few days of hypophysectomy, or at any time thereafter, if cortisone is withheld. If the adrenal glands have already been removed or destroyed by cancer there is a much greater risk of sodium depletion. Early signs of thyroid failure may be perceptible within a few weeks of operation (Li *et al.*, 1955). Obvious myxœdema takes

longer to appear owing to slow utilization of the existing pool of thyroid hormone within the body. After hypophysectomy for severe diabetic complications the impaired glucose tolerance becomes amenable to treatment by very small doses of insulin combined with subphysiological amounts of cortisone, e.g. 5 to 7.5 mg. a day. Hypertension is corrected and vascular degenerative lesions may be arrested (Luft *et al.*, 1955b).

COMPLICATIONS OF HYPOPITUITARISM

Only the complications due directly to endocrine failure will be discussed. Of these the most important are disturbances of consciousness ranging from hypersomnia to irreversible coma and the metabolic crises which often underlie them. Recent experience of the remarkable protective effects of cortisone in severe hypopituitarism suggests that the most important factor predisposing to coma in these patients is adrenal insufficiency. Consciousness seems to become unduly vulnerable to a variety of disturbing influences when deprived of adrenocortical hormones. Of the metabolic disorders, a liability to hypoglycæmia and to water intoxication is due directly to hydrocortisone deficiency. These disturbances may occur spontaneously or follow the incautious use of insulin tolerance or water excretion tests (see p. 619). It may be impossible to decide whether hypoglycæmia is the primary cause of coma or merely secondary to inanition after consciousness has already failed from some other cause. Coma is probably due to hypoglycæmia if muscle rigidity, extensor plantar responses or convulsions are present, in which case its effects may be irreversible or fatal if treatment is delayed.

Sodium depletion is an uncommon cause of crisis, although it is not yet known whether aldosterone continues to be secreted in the late stages of secondary adrenal atrophy. Low plasma sodium and chloride levels in these cases may be due to water (without sodium) retention rather than to sodium depletion, as suggested by recent metabolic studies (Wynn and Garrod, 1955).

Other factors known to precipitate hypopituitary coma are infections, a variety of drugs and anæsthetics, pituitary surgery, severe postural hypotension and pituitary apoplexy (hæmorrhage into a cystic pituitary adenoma). In hypopituitary coma due to infections or surgery, there is often no evidence of hypoglycæmia or disturbed water or electrolyte balance, and slight pyrexia or hypotension may be the only associated findings. As in primary myxœdema, hypothermia is a not infrequent late manifestation of hypopituitarism and is more likely to derive from thyroid than adrenocortical failure. Psychoses may also occur. Should diabetes insipidus already be present it will diminish or cease as failure of anterior pituitary function becomes severe.

DIAGNOSIS AND INVESTIGATION

The diagnosis of hypopituitarism is usually presumptive. It is based upon finding inadequate function of several pituitary hormones or their dependent glands, supported whenever possible by direct or indirect evidence of a

pituitary lesion. In many cases the diagnosis can be made with reasonable confidence from the history and physical findings, together with a few simple tests. The problem is more difficult in children with delayed puberty, in the early and selective phase of hypogonadism in adults, in the late myxœdematous stage, or when the likelihood of a pituitary lesion cannot be established directly or by inference from the history. The condition may not be recognized because of unawareness of its natural history or a too ready tendency to attribute gonadal or thyroid failure to primary causes without exploring the possibilities of pituitary disease. In suspected cases therefore, the pituitary fossa should always be x-rayed and an obstetric history obtained whenever appropriate.

With modern techniques certain pituitary functions can now be assessed with a fair degree of accuracy. Some procedures such as bio-assay of the thyrotrophic (Gilliland and Strudwick, 1956) and corticotrophic (Sydnor *et al.*, 1953) hormones are too laborious, insensitive at low levels, or uncertain for routine clinical application; others, such as the bio-assay of urinary gonadotrophins or the assessment of thyroid or adrenal response to stimulation by the respective trophic hormones can only be carried out in specially equipped centres. For many clinical purposes, however, it is enough to rely on a few simple investigations. These and some more elaborate procedures will now be discussed.

Growth hormone.—A deficiency of growth hormone can only be inferred. The signs are dwarfism with normal bodily and skeletal structure and proportions. Radiologically there is a great delay in ossification and in union of the epiphyses, depending to a certain extent upon the age of onset. In doubtful cases account should be taken of the family stature and reference made to height/age tables which include the percentile limits of normal (Wilkins, 1950b). There should be no confusion with cretinoid or hypothyroid dwarfism, in which the long bones are disproportionately shortened and the epiphyses often irregular or fragmented. The rare cases of hypopituitary dwarfism without other endocrine deficiencies cannot be distinguished during life from so-called primordial or 'Tom Thumb' dwarfism in which the end-organs appear to be irresponsive to growth hormone; nor is there any way of detecting an absence of this hormone arising during adult life.

The gonadotrophic functions.—Hypogonadism due to selective pituitary failure often can only be distinguished from primary hypogonadism by testicular biopsy or measuring the urinary gonadotrophin (mainly FSH) excretion. Gonadotrophin excretion is greatly increased in primary ovarian or testicular failure and is usually too low to be measured in pituitary hypogonadism. Since the assay may also be negative in healthy young women it is reliable in confirming hypopituitarism only after the menopause when the output of pituitary gonadotrophins should be high if pituitary function is intact. Lack of œstrogen secretion can be confirmed by cytological examination of a vaginal smear.

Corticotrophic function.—Pituitary-adrenal failure can be assessed by direct or indirect testing of adrenal function. Of the direct tests the easiest but least specific is the determination of urinary 17-ketosteroid excretion as a crude index of the combined adrenal and testicular functions. Adult values of less than 2 mg. a day (testicular function having already failed) are compatible with pituitary-adrenal failure, but may also occur in severe debilitating disease. In the female similarly low values are found in Addison's disease and some cases of untreated primary myxœdema.

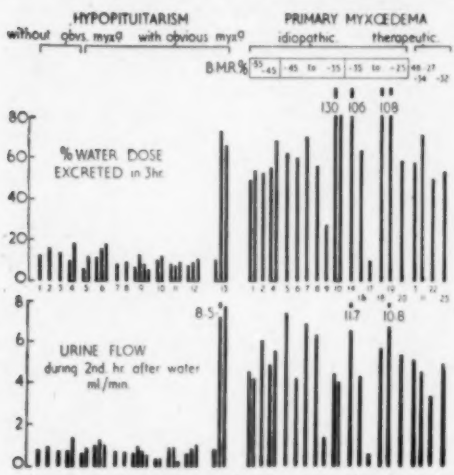

FIG. 3.—A comparison of water excretion tests in hypopituitarism and primary myxœdema (see p. 620).

A more specific index is the urinary output of 17-hydroxycorticoids (Reddy *et al.*, 1952) or of 17-ketogenic steroids (Norymberski *et al.*, 1953), both of which represent products of adrenal glucocorticoid secretion.

Very low values, rising significantly after corticotrophin infusion (Thorn *et al.*, 1953) or intramuscular corticotrophin gel, show that the adrenal failure is due to lack of pituitary stimulus. This increase of adrenal function after corticotrophin is also reflected by the response of the plasma 17-hydroxycorticoids (Christy *et al.*, 1955), and less specifically by the 17-ketosteroid excretion (Nabarro, 1954). The promptness and magnitude of the adrenal response to corticotrophin probably depends upon the duration and severity of the hypopituitarism (Christy *et al.*, 1955).

In routine clinical practice it is often necessary to depend upon one of the following indirect tests of adrenal glucocorticoid function.

Water excretion tests.—Recently there have been several modifications of the Robinson-Power-Kepler test directed more specifically to assessing adrenal glucocorticoid function (Garrod and Burston, 1952; Soffer and Gabrilove, 1952; Oleesky, 1953). All depend upon the inability of patients with severe glucocorticoid deficiency to excrete water with normal rapidity. The following has proved a useful screening test in a large series of cases. It should not be carried out if the plasma sodium is less than 130 mEq. per litre, for fear of inducing water intoxication (Wynn and Garrod, 1955).

The patient, recumbent throughout the test, is starved of food and fluids from 10 p.m. and given a light breakfast (1 piece of buttered toast and one cup of sweet tea at 6 a.m. in order to stave off hypoglycæmia). At 9 a.m. the bladder is emptied and 9 ml. of water per pound of body weight (20 ml. per kg.) are drunk slowly between 9 and 9.45 a.m. The bladder is again emptied at 10 and 11 a.m. and 12 noon and the hourly urine volumes and specific gravities are measured. Patients with

adrenocortical failure severe enough to give rise to symptoms seldom excrete more than 20 per cent. of the water dose in three hours and the urinary volume rarely exceeds 90 ml. during the second hour (fig. 3). If positive the test should be repeated after two days, giving 100 mg. of cortisone by mouth four hours before the water dose (50 mg. in children). Unless water excretion is greatly increased after the cortisone (more than 50 per cent. excretion in three hours) the failure cannot be attributed to adrenal insufficiency. The test is not valid in the presence of renal disease, heart failure, œdema, steatorrhœa or severe anæmia, and in these conditions the impaired water excretion is but little affected by cortisone. Diuresis is usually normal or only moderately impaired in primary myxœdema (fig. 4) and is normal in pure hypogonadism.

Fasting blood sugar.—Low fasting blood-sugar levels in patients with hypopituitarism are very suggestive of adrenocortical failure. The insulin tolerance test (Fraser and Smith, 1941) is then unnecessary. This last test should be avoided if severe hypopituitarism is suspected, for fear of causing irreversible hypoglycæmia; it is useful, however, in assessing milder cases.

The electrocardiogram.—Flattening or inversion of the T waves with normal or only slightly reduced QRS voltage is good presumptive evidence of adrenocortical failure if these changes can be corrected by cortisone (fig. 5). When myxœdema is also present the QRS voltage is very low and a normal pattern can only be restored by giving thyroid hormone as well as cortisone (fig. 5) (Garrod and Gilliland, 1954).

Thyrotrophic function.—Thyroid function is assessed by determining the basal metabolic rate and the voltage of the electrocardiogram, or preferably by measuring the uptake of radioiodine or the plasma protein-bound iodine (PBI) concentration. This latter estimation can only be made in one or two centres in this country. These tests, of which the PBI is perhaps the most sensitive, may be normal despite evidence of adrenal failure. Not infrequently the results suggest some degree of thyroid failure although clinically this may not be apparent (Peters *et al.*, 1954; Querido *et al.*, 1954). With obvious myxœdema the results cannot be distinguished from those of severe primary myxœdema, except for the plasma cholesterol concentration which is often normal; if this is less than 200 mg. per cent. the myxœdema is probably of hypopituitary origin (Van Arsdel and Williams, 1956).

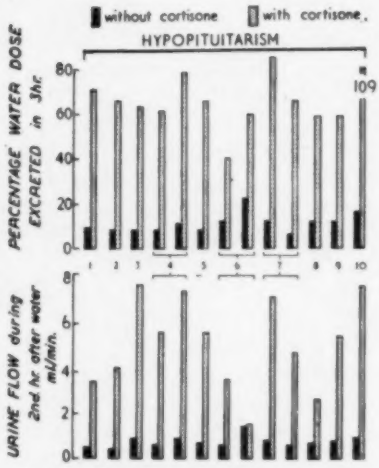

FIG. 4.—The effect of cortisone on water diuresis in 10 patients with hypopituitarism and secondary adrenal failure. 50 mg. cortisone was given by mouth three hours before the 2nd test. Further experience has shown that 100 mg. of cortisone four hours before the 2nd test is even more effective in restoring water diuresis.

Varying degrees of secondary pituitary failure may occur in untreated primary myxœdema. In order therefore to be sure whether myxœdema is primary or secondary it may be necessary to test the thyroid response to

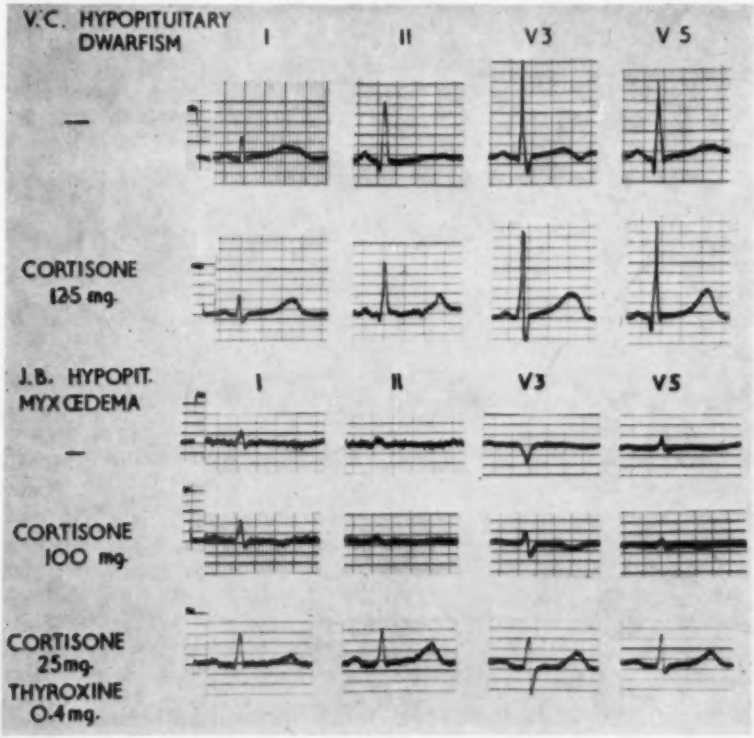

FIG. 5.—Electrocardiographic changes in hypopituitarism. Upper series from the patient shown in fig. 1. Lower series from the patient shown in fig. 2. In this last patient, who had adrenal and thyroid failure, cortisone alone did not correct the tracing.

stimulation by thyrotrophic hormone using the uptake of radioiodine as an index of thyroid activity (Querido and Stanbury, 1950; Fraser and Garrod, 1955). A positive response excludes primary myxœdema. Unfortunately, a negative response does not always exclude the possibility of hypopituitarism because in long-standing cases the thyroid gland can become irreversibly atrophied (Fraser and Garrod, 1955). If this test cannot be arranged, pituitary function should be reassessed after adequate treatment with thyroid hormone.

TREATMENT

General principles.—Treatment should aim at arresting the causative lesion whenever possible and replacing some of the missing hormones. Radical

therapy is directed towards curbing the growth, and relieving the pressure effects, of pituitary tumours. Further endocrine failure may thereby be prevented. Pituitary adenomas, unlike craniopharyngiomas, usually respond to irradiation. Surgery may be needed to save vision, to prevent brain involvement, or to evacuate a suprasellar cyst, but otherwise is seldom indicated. Endocrine therapy should be adapted to cover the deficiencies actually present, and in women need not aim at a perfect simulation of gonadal function. Theoretically, pituitary trophic hormones might be expected to offer certain therapeutic advantages over hormones of the glands they control. In practice, however, this is seldom so since hypopituitarism is usually irreversible; and such treatment, which is costly and uncomfortable from repeated injections, would need to be continued indefinitely.

Pituitary dwarfism and infantilism.—Unfortunately, growth hormone preparations are inactive in promoting growth in man. Several inches of growth, culminating in closure of the epiphyses, can, however, usually be achieved in hypopituitary dwarfs of pubertal or early postpubertal age by giving androgens (combined with œstrogens in females) over a period of several years. The possible advantages to be gained from initiating treatment with chorionic gonadotrophin (Heller and Nelson, 1948) are very doubtful (Spence, 1953). Testosterone is best given orally as methyltestosterone, 25 mg. a day, despite a very slight risk of jaundice. In males this creates adequate virility and improved muscular development and power. In females, 1 mg. of stilbœstrol, or 0.05 mg. of ethinyl œstradiol, is given daily for six to twelve months, after which cyclical therapy is started and the methyltestosterone is reduced to 10 to 20 mg. a day. As in adults cortisone or thyroid hormone should be avoided unless there is evidence of adrenal or thyroid failure.

Adult (acquired) hypopituitarism.—Male hypogonadism can be corrected, but without restoring fertility, by injections of long-acting testosterone, or by a daily oral dose of 25 mg. of methyltestosterone. This treatment, which should be continued indefinitely, also serves to restore adequate nitrogen balance and muscle strength. Pituitary hypogonadism in younger women is probably best treated by the smallest dose of œstrogens which will prevent atrophy of the breasts and sexual organs. Attempts to simulate the menstrual cycle by cyclical œstrogen and progesterone therapy are wasteful and probably unwise, except when there are strong psychological reasons. As in the male, a small dose of androgen, e.g. methyltestosterone, 10 to 20 mg. a day, helps to maintain sexual libido and muscle strength and is unlikely to cause masculinization.

Adrenal steroids should be prescribed only if there is adrenal failure; otherwise, by suppressing corticotrophic secretion, they will only accelerate atrophy of the adrenal cortex. If adrenal failure is present, however, the results of oral cortisone treatment are most gratifying. A pink colour returns to the skin, the blood pressure rises to normal, the appetite and nutrition improve, hypoglycæmia and water retention are corrected, and there is a

remarkable gain in both mental and physical vigour. The dose (given 12-hourly), need seldom exceed 25 mg. a day, and 12.5 mg. may be enough. A restriction of diet is sometimes needed to prevent excessive gain in weight. The cortisone should be increased, if necessary even to 200 mg. a day, to cover intercurrent infections, trauma, or emergency surgery, since the stress reaction normally mediated via the pituitary-adrenal axis cannot operate in these cases. Only rarely will the need arise for mineralocorticoid replacement (deoxycortone trimethylacetate or fluorohydrocortisone); nor should extra salt be required.

For reasons similar to those stated for cortisone, thyroid hormone is best reserved until the indications of thyroid failure are clear. In mild cases, 60 mg. of thyroid extract, or 0.1 mg. of l-thyroxine, may be enough, although treble this dose will probably be needed in frank myxœdema. The electrocardiogram is a useful guide in assessing whether the replacements of cortisone and thyroid hormone are adequate.

The treatment of hypopituitary coma and other crises has been described in detail elsewhere (Caughey and Garrod, 1954).

Fig. 1 and 2 are published by kind permission of Dr. Russell Fraser, who allowed me to study these patients.

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HORMONES AND THE BREAST

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In discussing this problem it is necessary to distinguish three processes: growth of the mammary gland, initiation of lactation ('lactogenesis') and maintenance or augmentation of lactation ('galactopoiesis').

Knowledge of the endocrine control of these processes is derived mainly from experimental studies on a number of different animal species. So great is the variation in response of these species to the hormone concerned that it would be imprudent to assume that the human breast behaves in a manner similar to the mammary gland in any particular species studied. For instance, in the cow and the goat, œstrogen alone causes extensive lobule-alveolar growth and may in certain circumstances be responsible for lactogenesis and galactopoiesis. In the mouse, the rat and the rabbit, very little alveolar growth is induced in the absence of progesterone, whilst in the dog, in the absence of progesterone, only slight growth of the mammary ducts occurs (Folley, 1955). Which of these species does the human resemble in this connexion?

It is impracticable to perform experiments on human individuals similar to those which have been undertaken on animals, and little precise knowledge therefore exists concerning the endocrine control of the human breast. It is proposed here to discuss briefly certain disorders of the breast in so far as they may throw some light on the extent to which hormones may influence the mammary gland.

ŒSTROGEN AND GROWTH OF THE MAMMARY GLAND

Sensitivity and resistance of the 'target organ'.—Some abnormalities of mammary growth depend, not upon the concentration in the circulation of the active hormone, but on the extent to which the tissues of the breast respond to normal concentrations of the hormone. Thus, some women are much distressed by the fact that their breasts are poorly developed but unfortunately œstrogen therapy, either topical or systemic, is quite ineffective. Occasionally one breast is normally developed whereas the other is significantly smaller and here again, topical administration of œstrogen, even to the extent of implanting œstrogen pellets into the breast tissue, fails to stimulate further development. To go to the other extreme, some adolescent girls or women who are not unduly overweight are embarrassed by the fact that their breasts are disproportionately large and pendulous. Here again no endocrine therapy is effective, and the problem is one for the plastic surgeon.

'*Premature thelarche*', a term coined by Wilkins (1950), refers to the enlargement, usually bilateral, sometimes unilateral, of the breasts during early girlhood. The condition may be transient and is unaccompanied by other signs of sexual precocity. According to Wilkins, it is due to 'sensitivity of the breast tissue to low levels of œstrogen secreted during early childhood'.

LACK OF ŒSTROGEN AND FAILURE OF MAMMARY GROWTH

Pituitary infantilism is a condition in which one or more hormones of the anterior pituitary are inadequately secreted. Growth hormone and gonadotrophin production is always involved and there may also be lack of thyroid-stimulating hormone and corticotrophin. The condition is relatively rare in women and when it occurs there is a symmetrically small body with lack of the secondary sex characters which normally develop under the influence of œstrogen. Thus the genitalia are poorly developed, there is complete lack of pubic and axillary hair and the mammary glands remain infantile. In cases of pituitary deficiency developing in adult life (for instance in *post-partum panhypopituitarism*—Sheehan's syndrome) there is atrophy of the mammary glands and defective lactation. On the other hand the failure may be primarily gonadal. Should this supervene during adult life there is seldom marked shrinkage of the breasts. If the ovaries, however, atrophy between birth and puberty ('*prepubertal ovarian failure*'), the lack of œstrogen influence becomes noticeable during adolescence. Epiphysial union may be delayed and with an inadequate growth hormone influence (in contrast to pituitary infantilism) the girl grows tall and lanky ('*ovarian eunuchoidism*'). The breasts do not develop and pubic and axillary hair is scanty.

Finally, failure of gonadal development may occur early in embryonic life before gonadal differentiation is due to begin. When this occurs the subsequent differentiation of the genital ducts, urogenital sinus and external genitalia follows the normal female pattern, although the lack of secondary sex characters, including mammary development, becomes evident as the age of puberty is reached. These cases, which are nearly always associated with stunting of growth, used to be referred to as '*ovarian agenesis*', but the recent introduction of the technique of nuclear sexing has shown that many of these individuals are genetic males and it would be more accurate to refer to the condition as '*gonadal agenesis*'. In all these conditions administration of œstrogen leads to a reasonable degree of mammary growth.

In another group of cases the effects of œstrogen are masked by overproduction of androgen. One example is the condition of congenital adrenal hyperplasia occurring in girls (*female pseudohermaphroditism*), as the result of which large quantities of adrenal androgens are produced from an early stage of embryonic life. The child grows rapidly and then becomes stunted as the result of premature closure of the epiphyses. Marked virilism is evident from early infancy and there is no mammary growth. Administra-

tion of cortisone suppresses the abnormal activity of the adrenal cortex and releases pituitary gonadotrophin so that the œstrogen produced by the ovary now leads to normal feminization with establishment of menstrual cycles and female breast development (Wilkins *et al.*, 1952). Other examples are the *adrenogenital syndrome* due to an adrenocortical tumour or hyperplasia producing excessive quantities of adrenal androgens and *virilizing tumours of the ovary* in which the clinical manifestations of virilism, including atrophy of the breasts, are presumably due to the production of an androgen by the ovary which, though it may not give rise to excessive output of urinary 17-ketosteroids, nevertheless suppresses the normal secondary sex characters due to œstrogen.

PREPUBERTAL ŒSTROGEN SECRETION AND MAMMARY GROWTH

The condition of premature thelarche has already been discussed. *Precocious puberty* in girls is nearly always 'constitutional'. This means that œstrogen is secreted at an early age and leads to breast development during the first decade. Very rarely, *granulosa-cell tumours* develop before puberty and lead to continuous and excessive œstrogen secretion and sexual precocity, including mammary growth. This, however, is not excessive in comparison with adult standards.

ABNORMAL ŒSTROGEN SECRETION IN ADULTS

Granulosa cell tumours occur more commonly in adults. They may be associated with menstrual disturbances due to continuous production of œstrogen, but no excessive breast development occurs. Such continuous œstrogen production is also seen in *metropathia hæmorrhagica* but this is seldom accompanied by mastalgia or mammary hyperplasia. *Mastalgia* and *fibroadenosis* are typically encountered during the premenstrual week or ten days. It has been suggested (Greene and Dalton, 1953) that this results from a high œstrogen/progesterone ratio. These authors advocate treatment with progesterone, and others have had satisfactory results by opposing the relatively excessive œstrogen influence with androgen therapy. Exogenous œstrogen administration in some cases leads to mastalgia with swelling and generalized nodularity of the breasts.

ŒSTROGEN AND MAMMARY GROWTH IN THE MALE (GYNÆCOMASTIA)

The list of conditions which may be associated with gynæcomastia is so long and diverse that, at first sight, it seems impossible to attribute this phenomenon to a single endocrine influence. Nevertheless, there is considerable evidence which suggests that œstrogen is the chief, if not the only, hormone to cause mammary growth in the male. Certainly exogenous application of œstrogen induces gynæcomastia. Other drugs and hormones have

occasionally been reported to cause gynæcomastia, such as certain batches of amphetamine (Tooley and Lack, 1949), which were subsequently found to be contaminated with an œstrogenic impurity (Mason and Morris, 1949), or digitalis which contains cardiac aglucones possessing the cyclopentophenanthrene chemical structure characteristic of steroid hormones (Calov and Whyte, 1954). Among the other hormones are chorionic gonadotrophin and methyltestosterone; the former does, and the latter may, cause hyperplasia of the Leydig cells of the testis.

Gynæcomastia is a characteristic feature of testicular and *adrenocortical tumours*. It is extremely rare for the latter to give rise to endocrine manifestations in the male but gynæcomastia is usually the first of these signs. Gynæcomastia has also been reported as occurring in connexion with most of the various types of testicular tumours such as interstitial cell tumour, chorion-epithelioma, teratoma and seminoma and the only case of Sertoli-cell tumour described as occurring in a human male (Teilum, 1946). Œstrogen has been extracted from the adrenal cortex and it seems likely that these rare adrenocortical tumours in males produce œstrogen. The source of œstrogen in testicular tumours is more interesting. There is general agreement that the normal testis produces œstrogen, and the consensus of opinion favours the interstitial cell as being the source of œstrogen and androgen. A number of Sertoli-cell tumours have been described in dogs (Huggins and Moulder, 1945), and one case of a *Sertoli-cell tumour* occurring in a man has been reported by Teilum (1946). Feminization, including gynæcomastia, occurred both in the dogs and the man. Nevertheless, there is no general support for the idea that testicular œstrogen is produced by the Sertoli cells. On the other hand, Maddock *et al.* (1952) found that the œstrogen secretion of two men, whose only remaining testicular structure was clumps of Leydig cells, was significantly higher than castrate levels. They also administered chorionic gonadotrophin to seven normal men and found a striking increase in œstrogen secretion. Testicular biopsy showed hyperplasia and signs of increased secretory changes in the Leydig cells and seminiferous tubule damage. Presumably the increased production of androgen and œstrogen by the Leydig cells led to suppression of pituitary gonadotrophin and degeneration of germinal epithelium. Hall and Thomas (1955) examined material obtained by testicular biopsy in the Department of Endocrinology at Guy's Hospital in over 50 cases of gynæcomastia and found the typical picture to be one of hyperplasia and clumping of the Leydig cells. Gynæcomastia has occasionally been found in association with *interstitial cell tumours of the testis* (Melicow *et al.*, 1949). It has also been reported in connexion with *seminomas*, *teratomas* and *chorion-epitheliomas*. This is probably due to the production of chorionic gonadotrophin which would stimulate the interstitial cells to produce androgen and œstrogen.

Another condition of interest in this connexion is the feminine type of

male pseudohermaphroditism in which the individual superficially appears to be a normal female with full breast development, although the gonads are discovered to be testes consisting of small tubules containing no germinal epithelium, but with an excess of Leydig cells which may be producing œstrogen only, for there is evidence that the source of the urinary 17-ketosteroids in these cases of 'feminized testicles' is entirely the adrenal cortex (Boute *et al.*, 1952).

It is difficult to explain the development of gynæcomastia in some individuals castrated before puberty (Wagenseil, 1927), and in those in whom, as the result of congenital abnormalities, infection or trauma, the testis completely degenerates before puberty (*'functional prepubertal castration'*). It must surely be assumed that in these cases the œstrogen is produced by the adrenal cortex, if indeed the gynæcomastia is due to œstrogen or a disturbed androgen/œstrogen ratio. In testicular failure which develops during puberty (*Klinefelter's syndrome*) gynæcomastia appears only in those individuals who reach the later stages of puberty before testicular degeneration takes place. They therefore tend to have a normal masculine habitus, in contrast to the cases in which testicular failure occurs early in puberty when eunuchoidism without gynæcomastia is the characteristic picture. Presumably the adrenal cortex is not involved in this condition but the œstrogen in the older patients is derived, together with androgen, from the clumped Leydig cells.

Gynæcomastia is also seen in association with severe *liver disease* and is believed to be due to failure of the liver to conjugate œstrogen so that relatively high concentrations of the active hormone are in circulation. This is not to be confused with the gynæcomastia reported by Kark *et al.* (1951) in cases of severely undernourished cirrhotics during treatment with high-protein, high-calorie diets, which they suggest may be due to the introduction of arginine in adequate quantities into the diet. This *'re-feeding gynæcomastia'* has been a prominent feature in the picture which accompanies improved nutrition in repatriated prisoners-of-war. The gynæcomastia is transient and consists often of hard subareolar plaques; it may be accompanied by mild orchitis and return of libido. A similar form of gynæcomastia is seen in patients recovering from *debilitating diseases*, such as thyrotoxicosis, sprue and severe diabetes mellitus. Polymenakos (1952), who was a prisoner-of-war during the occupation of Greece, refers to this type of gynæcomastia as 're-adoleseent'. Indeed, some degree of gynæcomastia occurs in 80 per cent. of *boys at puberty*. It is usually transient although it may persist and require plastic surgery. It is probably due to initiation of functional activity of the Leydig cells with some temporary imbalance of their androgen/œstrogen ratio of production.

THE BREAST IN PREGNANCY

Although œstrogen alone may control mammary development in the non-

pregnant individual it seems likely that both œstrogen and progesterone are necessary for the full maturation of the mammary duct system and the lobule-alveolar structures that are essential for the eventual secretion of milk. Indeed, one of the important causes of defective lactation is that the mammary tissue has been insufficiently prepared to respond to the processes which lead to lactogenesis.

LACTOGENESIS

The following 'tentative theory' of the mechanism of induction of lactation has been put forward by Folley (1955). Relatively low circulating levels of œstrogen activate the lactogenic and galactopoietic functions of the anterior pituitary. This possibly accounts for the fact that in some of the cases in which gynæcomastia develops some secretion of fluid may be expressed from the nipple. High levels of œstrogen inhibit lactation. The presence of progesterone deprives even low levels of œstrogen of their lactogenic properties. Thus, lactogenesis during pregnancy is doubly prevented by high œstrogen titres and the presence of progesterone. At parturition not only is the inhibitory influence of progesterone removed, but also the withdrawal of œstrogen resulting from the separation of the placenta permits lactogenic titres of œstrogen to be achieved. Lactogenesis, however, also involves the presence of one or more pituitary hormones, notably, if not solely, prolactin. Administration of high doses of œstrogen therefore at the time of parturition will inhibit lactation, but once lactation has been initiated (i.e. once lactogenesis has occurred) it is normally maintained by the mechanical process of suckling, in the absence of which the breasts will become engorged and painful during the first few days of parturition. Œstrogen given after parturition has taken place will suppress or prevent this breast engorgement.

'*Spontaneous lactation*'.—A syndrome consisting of spontaneous lactation, amenorrhœa and low urinary gonadotrophin excretion has been described by Argonz and del Castillo (1953) and by Forbes and her colleagues (1954), whilst individual cases of this syndrome have been reported by others (Ahumada and del Castillo, 1932; Foss and Short, 1951). By 'spontaneous lactation' is meant lactation occurring not immediately following parturition. In eight out of the 15 patients of the Forbes series there was evidence of a pituitary tumour and in three the tumour was proved by biopsy to be a chromophobe adenoma. According to Cushing (1932-33), a chromophobe adenoma is always pre-eosinophilic in type, and eosinophil cells produce prolactin and growth hormone. It seems probable that in this syndrome lactogenesis is due to abnormal production of prolactin and that galactopoiesis is maintained by growth hormone. Acromegaly is occasionally accompanied by spontaneous lactation.

It has recently been reported (Winnik and Tennenbaum, 1955; Gäde and Heinrich, 1955; Sulman and Winnik, 1956; Marshall and Leiberman,

1956) that chlorpromazine therapy may be accompanied by lactation. Sulman and Winnik suggest that this is due to inhibition of hypothalamic activity, with release of prolactin and growth hormone.

GALACTOPOIESIS

According to observations on lactating cows, prolactin has little if any galactopoietic activity and the maintenance of lactation is mainly under the control of growth hormone (Cotes *et al.*, 1949). Attention has already been drawn to the condition of spontaneous lactation, to the occurrence of lactation in acromegaly, and to the secretion of both prolactin and growth hormone by the eosinophil cells of the pituitary.

Folley (1955) has reviewed the endocrine control in animals. He points out that the pituitary-adrenal axis is necessary for the maintenance of normal lactation although in the cow corticotrophin seems to have an inhibitory rather than a stimulant effect (Cotes *et al.*, 1949). In adrenalectomized rats galactopoiesis can be maintained by a combination of cortisone and deoxycortone (Cowie, 1952). Cowie and Tindal (1955) have found that very small doses of chlorohydrocortisone can maintain complete lactation in such animals. Both iodinated casein and l-thyroxine can increase the milk-yield in cows (Bailey *et al.*, 1949).

It must be realized that these phenomena may well be species-specific and may not apply to the human individual in whom no satisfactory endocrine treatment for defective lactation has so far been found.

Persistent lactation following weaning occasionally occurs. Its association with atrophy of the uterus and ovaries and amenorrhœa was described by Chiari *et al.* (1855) and by Frommel (1882). This combination is referred to as the *Chiari-Frommel syndrome*, and is exceedingly rare; it is less uncommon to find persistent lactation without genital atrophy. Amenorrhœa, however, is not infrequently seen although menstrual cycles are normal in some cases.

CANCER OF THE BREAST

At the present moment it is prudent to refrain from embarking too readily on hypothetical explanations of the action of hormones in either the development or the treatment of cancer of the breast. A recent review by an acknowledged expert on this subject is commendably cautious (Nathanson, 1954). It may be tempting to state dogmatically that endogenous œstrogen is an important factor in mammary carcinogenesis, and that regression of the growth process may be expected to follow administration of androgen (or even high doses of œstrogen) given to suppress gonadotrophic activity and therefore to induce ovarian atrophy in premenopausal women. It may be equally tempting to point out that oöphorectomy, especially in combination with adrenalectomy, removes the source of endogenous œstrogen, and that hypophysectomy leads to ovarian and adrenocortical atrophy. It seems unlikely, however, that the problem is quite so simple. For instance, it appears that there are tumours which are 'hormone-dependent' and other tumours which are autonomous. It is possible that the reaction of any

individual cancer cell depends upon the endocrine 'milieu' at that particular moment and on the response of the more resistant cells, which may differ from, or indeed be precisely opposite to, that of the more vulnerable cells that may be, or may have been, promising targets for some particular endocrine therapeutic attack. (The vagueness of the phrasing of this last sentence shows how dangerous experimentally unsupported theories may be in this particular field.)

With regard to endocrine therapy it should be observed that it has become fashionable to employ enormous doses of œstrogen, whenever this hormone is used. There seems to be no serious evidence that doses in excess of 15 mg. of stilbœstrol daily are required. The dose of androgen seems to be in the region of 100 to 200 mg. of methyltestosterone daily.

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HORMONES AND HUMAN FERTILITY

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Although the employment of medicinal substances for the promotion of fertility in human beings is of great antiquity, there is no doubt that until recent times such treatment has been wholly empirical and probably almost wholly ineffective. The growth of knowledge of the hormones and of their actions, and especially of the important parts they play in reproductive processes, has led to the hope, which has often been expressed, that suitable endocrine treatment might be of value in the promotion of human fertility. It is not unfair to say that, for the most part, these hopes have remained unfulfilled, and that much of the hormonal treatment that has been employed has continued on an empirical rather than a physiological basis.

MALE INFERTILITY

Hormones have been employed for three purposes for the promotion of male fertility: to promote sex drive; to promote spermatogenesis; and to improve spermatozoal activity. The psychological aspects implied in the first of these purposes will not be considered in this article.

SPERMATOGENESIS

The employment of various hormone preparations to overcome defective spermatogenesis has now been going on for a long time, mostly without success. On theoretical grounds, it is clear that only when hormonal insufficiency is responsible for the failure of spermatogenesis can useful results be expected from hormone replacement therapy, and in general this is borne out in practice. Since most subfertile men show no obvious hormonal deficiencies, however, and increasing knowledge derived from the more frequent use of testicular biopsies shows that patterns of tubular disorganization unlikely to be affected by any form of treatment are common in such men, it is not surprising that neither hormonal nor any other form of treatment produces useful results, except occasionally. On the other hand, hormone therapy for hypogonadotrophic eunuchoids may give very gratifying results.

Thus, Maddock *et al.* (1952) reported on three such men who received 5000 i.u. of chorionic gonadotrophin thrice weekly for three or more months: in one of these patients a testicular biopsy showed spermatogenesis proceeding to all stages, although in another it proceeded only to the spermatocyte stage. Simmons (1952) reported the results of treatment of four similar eunuchoids with chorionic gonadotrophin and sublingual methyltestosterone. Both the wives of the two married men in this group became pregnant. In a more recent report, Simmons (1954) had increased his series of patients to 11, all of whom now have normal semen.

The use of testosterone in the treatment of male eunuchoids would seem also to lead to spermatogenesis in at least some patients, as well as to the development of normal secondary sex characters. Four patients who showed such a response were described by Hurxthal *et al.* (1949); one of these subsequently had two children and another also had a child (the other patients were unmarried). I reported a similar response to testosterone with the development of full spermatogenesis persisting long after the last implantation in a man who, before treatment at the age of 27, had genital development only of a degree to be expected in a boy of about 14 (Swyer, 1951).

The objection has been raised that the alleged results of treatment in these patients are, in fact, no more than the spontaneous development of late puberty, which occurred—or would have occurred—in spite of treatment. It seems unlikely that this could be true for all the patients reported. For example, one of the patients of Hurxthal and his colleagues was still eunuchoidal at the age of 43; after testosterone treatment he became fertile, and the possibility that this change was independent of the treatment seems far less likely than that it was caused thereby. Similar arguments could be applied to quite a number of the other reported cases.

When we come to consider the uses of hormones in dealing with defective spermatogenesis, or deficient spermatozoal activity, in non-eunuchoidal men, disappointment and controversy really begin to appear. A good deal of use has been made of the available gonadotrophins—chorionic and equine—and considerably less of pituitary preparations which are not commercially available, and it is fair to say that the results achieved have been almost universally negligible. When due account is taken of the marked variability in semen samples shown by many men, this statement becomes particularly true and, unless a proper datum-line has been secured by repeated examination before treatment, apparent improvement after treatment cannot be accorded any significance. This objection can certainly be raised to some of the favourable reports in the literature both on gonadotrophic and other forms of treatment of seminal deficiencies.

Testosterone has been employed for the treatment of defective spermatogenesis in two ways: administration in high dosage to produce temporary testicular suppression, to be followed by a rebound on cessation of treatment; and administration in low dosage for an expected direct 'stimulatory' action on spermatogenesis.

The historical background of the 'rebound effect' of testosterone in high dosage may be summarized as follows. The fact that testosterone in sufficient dosage would depress spermatogenesis has been known for many years; in 1950, Heller *et al.* reported the findings in serial testicular biopsies made on patients given such large doses of testosterone, and demonstrated that the initial degenerative changes immediately following the course of treatment were succeeded, on its cessation, by repair and, in some patients, by the development of a testicular structure appreciably more 'normal' than before treatment.

In a series of reports, Heckel and his colleagues (Heckel, 1951; Heckel, Rosso and Kestel, 1951; Heckel and McDonald, 1952a, b) reported the results of testosterone administration in 79 subfertile men, of whom 72 were 'oligospermic' (though the total number of spermatozoa in ejaculates before treatment was as high as 60 million in some patients) and seven were azoospermic. Testosterone caused depression of spermatogenesis in all the oligospermic men, and from the data on 45 of the men it was concluded that 23 showed a rebound phase, in which the sperm count rose well above the levels before treatment, although it subsequently fell again in seven patients; no rebound phase was observed in 22 patients. There were 10 pregnancies, of which, by the time of reporting, five had resulted in healthy babies, and two had terminated in abortion at four months.

These claims by Heckel and his colleagues naturally aroused a good deal of interest, and testosterone has now been used in this way by many workers. There have, however, been few further reports in the literature and it is well known that the general reaction has been one of disappointment. Simmons (1954) states that the replies to over eighty questionnaires sent to members of the American Society for the Study of Sterility were unfavourable to the rebound technique. My own limited experience with this technique has shown that a rebound does indeed exist in a few cases, but these have comprised less than 20 per cent. of the men so treated, and certainly not the 50 per cent. reported by Heckel and McDonald (1952a).

There is some evidence that testosterone administration in low dosage, by the implantation of pellets, may have a beneficial effect on spermatogenesis in some patients. Okbi (1949) implanted two pellets of 100 mg. each in ten men complaining of sterility and obtained what appeared to be improvement of the seminal fluid in eight of them. Since repeated analyses before treatment were not made, however, in most of these cases, the conclusions are open to doubt.

In a more extensive series, I reported (Swyer, 1953a, b) on the effect of implanting two and three 100-mg. pellets of testosterone subcutaneously in 56 men presenting various kinds of seminal deficiency. These men received a total of 67 implants: 28 of 200 mg. and 39 of 300 mg. There appeared to be improvement in the seminal fluid in 28 cases (12 received 200 mg., 16 received 300 mg.); no change in 22 cases; and a deterioration in 6 others (1 received 200 mg., 5 received 300 mg.). There were no significant effects on volume and seminal morphology but there was a highly significant increase in motility with both doses of testosterone, and in density with 300-mg. implants. Extreme oligospermia invariably failed to respond to treatment. The wives of 20 men became pregnant on 22 occasions, all within six months of implantation; five pregnancies ended in abortion (22.75 per cent.), the remainder going to term.

As a result of these observations I suggested that moderate depression of sperm density (15 to 20 million/ml.) or poor motility (other than extreme asthenospermia) with fair or good density offered the best chances of improvement after testosterone implantation.

SPERMATOZOAL MOTILITY

Our knowledge of the factors necessary for the development of normal spermatozoal motility and for the persistence of this activity is extremely scanty. Consequently, the causes of deficient sperm activity are unknown, treatment is empirical, and the results correspondingly disappointing.

I know of no effective means of influencing persistent true necrospermia (wherein motile spermatozoa are never found). Douglas (1946) claimed that testosterone was often helpful when the sperm count was normal but activity was deficient, and rather more convincing evidence of this was obtained from my observations (Swyer, 1953a, b). Sometimes the administration of desiccated thyroid helps (the use of thyroid is further discussed on p. 639). An increase in progressive spermatozoal motion after the administration of amphetamine has been claimed by Schwartz and Zinsser (1955). My limited experience with this drug is not very encouraging, although in one or two cases it would seem that an ejaculate produced 10 to 12 hours after taking 5 mg. of dexamphetamine sulphate has shown rather better spermatozoal activity than those obtained previously.

FEMALE FERTILITY

Nothing will be said about the purely empirical and non-specific use of hormones for the promotion of fertility in women, but consideration will be given to the following main purposes of hormone treatment for female infertility: the correction of genital hypoplasia; menstrual disturbances, leading to the failure of ovulation or its infrequent occurrence; endometrial dysfunction, causing nidatory failure; threatened and repeated abortion; and for the prophylaxis of late pregnancy toxæmia.

GENITAL HYPOPLASIA

There is no doubt that this condition is diagnosed too often and on inadequate evidence. Moreover, when it really does exist, unless accompanied by other evidence of ovarian insufficiency, it is most commonly due to target organ failure and is therefore scarcely amenable to treatment. The administration of œstrogens in moderately high dosage and in interrupted courses does sometimes lead, however, to growth of the uterus and cervix, which may increase the chances of conception at a later date.

MENSTRUAL DISTURBANCES

A full treatment of this subject is clearly out of the question. I have described the use of oral hormonal therapy for various menstrual irregularities elsewhere (Swyer, 1950). There are many reports in the literature, both favourable and unfavourable, on the use of various hormone treatments for the promotion of ovulation in women.

In a recent survey of the use of steroids and gonadotrophins in gynæcology, Taylor (1953) has divided the indications for these various substances into 'acceptable', 'probable occasional', and 'doubtful' categories. So far as gonadotrophins are concerned, he regards all the indications as doubtful, listing sterility due to failure of ovulation as number one. Although most critical studies have failed to demonstrate conclusively the ability of gonadotrophins to stimulate ovulation in women, it is admitted that the occasional occurrence of pregnancies during or following a course of gonadotrophin

treatment keeps open the possibility that in special circumstances the desired result may actually be produced.

DISTURBANCES OF CERVICAL FUNCTION

By preventing the ready ingress of spermatozoa into the cervical canal and their survival therein, disordered cervical function is a common contributory cause of infertility. At the time of ovulation the normal cervix develops a free flow of watery mucus into which the spermatozoa may penetrate and in which they may survive for prolonged periods of time. The secretion of such a mucus may fail to occur, either as a result of relative œstrogen deficiency or, perhaps more likely, of a relatively inadequate endocervical response to otherwise normal œstrogenic stimulation.

The practice of administering small doses of œstrogen during the first half of the menstrual cycle to overcome this disorder is widely used, and there is no doubt that, with such treatment, the flow of cervical mucus at the time of ovulation may be improved and a previously negative post-coital test become positive. Unfortunately, in a number of women the dose of œstrogen required to improve the cervical mucus is sufficiently large either to inhibit or to postpone ovulation, and the treatment thus defeats its own end. When this is the case, the more usual course of œstrogen, beginning about the fourth day of the cycle and continuing for 10 to 14 days can be replaced by a much shorter course, beginning three or four days before the expected day of ovulation but consisting of a higher dose, such as 2 mg. of stilbœstrol or 0.1 mg. of ethinylœstradiol daily, instead of 0.2 mg. or 0.05 mg. respectively daily as given over the longer course. Even this modified treatment, however, may inhibit ovulation in some women. The possibility of more local treatment, as by intra-cervical injection of œstradiol benzoate just before the time of ovulation, is worth considering in such cases, although it has obvious disadvantages.

ENDOMETRIAL DYSFUNCTION: NIDATORY FAILURE

Routine endometrial biopsies, taken shortly before the expected onset of the menstrual period, occasionally reveal a degree of development corresponding to a phase of the cycle earlier than the immediately premenstrual phase. These findings are usually interpreted as being indicative of progesterone deficiency, or of deficient endometrial response to normal progesterone levels, and it is generally agreed that in such circumstances failure of nidation of a fertilized ovum may be the cause of sterility.

There can be no doubt that this is not a common or important infertility factor, and it is quite uncertain that pregnancies in such patients, following the administration of progesterone or ethisterone during the second half of the cycle, in order to increase the degree of secretory development, are, in fact, to be attributed directly to the treatment. It is a matter of experience that a biopsy specimen indicative of progesterone deficiency may later be followed by an entirely normal one, even in the absence of any treatment.

When repeated premenstrual biopsies show a real deficiency of progestational development, however, it is certainly reasonable to administer progesterone in some form or other during the second half of the cycle and, when this is done, the biopsy may assume a more normal pattern. In these circumstances, the administration of the hormone would be a reasonable measure for the promotion of fertility.

THREATENED AND REPEATED ABORTION

That spontaneous abortion is commonly due to hormonal deficiencies has long been a popular belief and, as a corollary, the exhibition of various hormones, mostly progesterone, œstrogens or desiccated thyroid, has been extensively advised in an attempt to deal with these conditions. There is wide variation of opinion on the efficacy of hormone treatment for spontaneous abortion. This is scarcely surprising, since it seems probable that hormone deficiency is a relatively uncommon cause of abortion. The studies of Hertig and Rock (1949) suggest that germ plasm defects of various kinds are probably a far more common cause of spontaneous abortion than endocrine factors. Nevertheless, Peters and his colleagues (1948) found evidence of a decrease in the serum protein-bound iodine (PBI, a measure of circulating thyroid hormone) in some women threatening to abort; and in seven patients in whom PBI concentrations of less than 6 mcg./100 ml. were discovered early in pregnancy, thyroid treatment raised the level to normal in all cases, the pregnancies continuing without interruption—as, of course, they might have done anyway. Furthermore, Bender (1948) has shown that when progesterone is given to women with low pregnanediol excretions who are threatening to abort, the salvage rate is materially increased; whereas when it is withheld from women with high pregnanediol levels who are threatening to abort a similar improvement in salvage rate is obtained. The belief is prevalent among some of the French workers that insufficiency of œstrogens, of progesterone, or both, may commonly occur in pregnancies threatening to abort. These workers believe that hormone treatment should be based on the results of urinary steroid analyses—œstrogen, progesterone, or both, being given according to the apparent needs.

Both œstrogens and progesterone have been used for the prophylactic treatment of repeated or so-called habitual abortion. Smith (1948) used stilbœstrol according to an incremental dosage scheme, and Bishop and Richards (1952) used progesterone implants, a success rate of the order of 80 per cent. being claimed for both treatments. On the other hand, Bevis (1951) used no specific treatment but merely subjected his patients to extensive investigation; he, too, had a success rate of about 80 per cent. A study by Swyer and Daley (1953), in which the outcome in a control group who received no specific therapy was compared with that in another given progesterone implants, using the same technique as Bishop and Richards, showed no significant difference between the two groups. Moreover, these authors were unable to find any convincing evidence of proges-

terone deficiency in these patients. On the other hand, Jones and Delfs (1951), after studying extensively the endocrine patterns in women with histories of abortion, based their treatment (with thyroid, progesterone and vitamin E) on the findings of apparent deficiencies of these factors; 85 per cent. of the treated hormone-deficient patients went to term, as compared with only 22 per cent. of the untreated hormone-deficient patients. But, since only 50 per cent. of the untreated patients not deficient in hormone went to term, treatment may have had a psychological, as well as—or even instead of—an endocrinological effect.

Prophylactic antenatal use of stilbœstrol.—It was claimed by Smith and Smith (1949) that the antenatal administration of stilbœstrol according to an incremental dosage scheme to 387 primigravidæ had several significant beneficial effects on the course and outcome of pregnancy, as compared with those of 555 untreated 'controls'. There was a reduction in the incidence of toxæmia of late pregnancy, and when toxæmia occurred, it did so later in the pregnancy and was less severe. Prematurity and postmaturity were less often encountered, and there was a reduction in the incidence of unexplained stillbirths and fœtal deaths. There have been some recent reports of attempts to confirm these results—all of them negative. Thus, Ferguson (1953) repeated the experiment with more adequate controls and could find no effect on pre-eclampsia, prematurity and fœtal survival in his 199 treated patients as compared with 203 control patients given placebos. Dieckmann *et al.* (1953) reported similar results in a large and well-controlled series, whilst Swyer and Law (1954) have also been unable to find any difference between control patients on placebos and patients treated with stilbœstrol.

ADRENAL HYPERPLASIA AND FERTILITY

Following the remarkable studies of Wilkins and his colleagues (1950a,b, 1951, 1952a,b,c) on the effects of cortisone administration to patients with congenital adrenal hyperplasia, a new interest has arisen in the possibility that certain forms of sterility, both male and female, may be due to this cause and may therefore be amenable to hormone therapy. It was suggested by Jones *et al.* (1953) that women with symptoms indicative of mild adrenal dysfunction, such as amenorrhœa or oligomenorrhœa, hirsutism, acne and slightly elevated 17-ketosteroid excretions, might respond to cortisone therapy by ovulation. The subject has recently been elaborated further by Jones and Jones (1954) who distinguished four groups of cases with congenital adrenal hyperplasia: (1) female pseudohermaphroditism, (2) postnatal virilism, due to adrenal hyperplasia, (3) post-puberal hirsutism, infertility and oligomenorrhœa with elevated 17-ketosteroid excretion, and (4) as in (3), but with normal 17-ketosteroid excretion. Examination of the enlarged adrenals from 15 patients in groups (1) and (2) showed hyperplasia of the reticular zones, with lack of the zona fasciculata. In normal adrenals, the latter zone contains birefringent lipids and the former does not; but in these hyperplastic adrenals the distribution is reversed. The fascicular zone

is believed to produce hormones of the glucocorticoid type, and it is therefore argued that absence or functional incompetence of this zone is associated with the disturbed hormonal pattern.

Jailer (1953) has suggested that the adrenal in this condition is incapable of adequate hydroxylation of the 11 and 21 positions of C-21 steroids and this leads to the production by the adrenal of an incomplete cortical steroid, 17-hydroxyprogesterone, instead of the normal production of 17-hydroxycorticosterone (hydrocortisone). In consequence, the anterior lobe of the pituitary gland secretes excessive quantities of adrenocorticotrophic hormone (ACTH), since it is not subjected to the inhibiting influence of hydrocortisone, whilst 17-hydroxyprogesterone is thought to be incapable of inhibiting pituitary ACTH secretion. The overstimulated adrenal cortex thus converts large quantities of steroid precursors into 17-hydroxyprogesterone which, in turn, is metabolized to form substances excreted as 17-ketosteroids and also into pregnanetriol, the excretion of which has been described in this disease.

The administration of cortisone in adequate dosage inhibits the excessive pituitary ACTH secretion, and so reduces the excessive activity of the adrenal cortex. In the group of patients studied by Jones and Jones (1954), a daily dose of 50 mg. of cortisone orally for the first month, followed by 25 mg. subsequently, led to the occurrence of ovulation in all the 16 patients in group (3), five out of 10 becoming pregnant. Of the patients in group (4), all have ovulated and, at the time of reporting, all but four out of 11 had conceived.

The studies of Wilkins and Cara (1954) on the effects of cortisone therapy on testicular development in boys with virilism due to adrenal hyperplasia, encourage one to hope that this treatment will prevent the sterility which is otherwise found in adults who have suffered from this condition.

THE THYROID AND FERTILITY

Writing in 1936, Chute stated:

'Last, but far from least, the oral administration of thyroid is indicated in all cases presenting even a low normal metabolism, and obesity. In some way it also seems to act as a most valuable adjuvant in pituitary gonad cases, possibly because it activates sluggish bodily processes. It is one of the most valuable aids in sterility, either alone or in combination with other therapy '.

Kreutzmann (1940) was also impressed with the value of thyroid medication in the treatment of male sterility. He found 15 per cent. of 45 men to have a basal metabolic rate between -10 per cent. and -18 per cent.; following thyroid therapy, it was claimed that all these men produced pregnancies. Many other subsequent writers appear to have been favourably impressed by the value of thyroid medication, mostly on purely empirical grounds. It is notable, however, that critical studies are almost totally lacking in the literature, and a salutary article by Tyler (1953), entitled 'The thyroid myth in infertility', puts the case strongly against the indiscriminate administration of desiccated thyroid, or thyroxine, in cases of infertility, and the facile supposition that subsequent pregnancies are the direct result of this treatment. It is doubtful if significant hypothyroidism is any more prevalent among persons complaining of infertility than among the rest of the population and it is certain that the indiscriminate administration of thyroid

hormone, either in large or in physiologically insignificant doses, is wholly to be deplored.

CONCLUSIONS

Clearly defined endocrine causes of infertility are relatively uncommon. When found, certain of these are amenable, to a greater or lesser extent, to hormone treatment. In the absence of endocrine infertility factors, the empirical administration of hormones has little or no effect on the promotion of fertility, and can only be condemned.

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HORMONES AND DISTURBANCES OF GROWTH IN CHILDHOOD

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Tissue organization and sex differentiation in the embryo involve action based upon hormones, genes, enzymes, and organizers. Maternal ovarian hormones are not used in the direct building up of the fœtus, although rarely an influence can be traced, as in the case of arrhenoblastoma during pregnancy reported by Brentnall (1945) in which the female baby was to some extent intersexual at birth. After the first impetus of early embryonic growth, the fœtal hormones are essential for its self-development.

Growth abnormalities of endocrine origin should not lead to any confusion concerning such clinical abnormality of growth as represented in Mongolism or gargoylism or any other forms of true hereditary anatomical variations. Thus, diagnosis in the neonatal period, or later, calls for a precise understanding of which forces—endocrine or genetic—have led to the problem presented.

FŒTAL HORMONE DISTURBANCES

Fœtal growth proceeds on normal lines so long as the endocrine pattern is normal. Slight or serious distortions can occur, the most significant effects occurring in sex maturation. Under a barrage of its own maladjusted hormones true hermaphroditism (rare) or pseudo-hermaphroditism (not rare) may occur. Initial gonadal abnormality may precede, or develop concurrently with, these anatomical changes, which may or may not be recognizable at birth. Agenesis of the ovaries or testes may only be detected clinically at a later stage. Congenital anencephaly is associated with marked adrenal hypoplasia.

Fœtal growth is normally directed by its own neuro-pituitary-endocrine system. If the fœtal thyroid gland fails there is an ample trans-placental supply of thyroxine from the healthy mother. Maternal anti-thyroid medication will not usually impair fœtal growth, but the raised and responsive fœtal thyrotrophic hormone will cause its own thyroid gland to enlarge *in utero*. This 'congenital goitre' is temporary only. If the mother has latent or manifest diabetes mellitus the fœtus is endocrinologically influenced towards overgrowth and higher birth weight at full term (the so-called 'Cushingoid' baby).

Fœtal gigantism.—There are several substantiated examples of a birth weight over 6000 grammes (13 lb.). The largest verified was a stillborn infant who weighed 10,943 grammes (24 lb.). The heaviest recorded live birth weight is 7,824 grammes (17 lb.). The various possible reasons for

big babies include the endocrine aspects in maternal diabetes mellitus and maternal obesity, and genetic factors in the family (Schuyer, 1955).

Infantile pseudohermaphroditism.—In this condition the female baby at birth is noted to have an enlarged clitoris (fig. 1). Vomiting, usually projectile, soon occurs, and some increased pigmentation may be observed: e.g. at the nipples. General growth may be severely disturbed, and a marasmus-like state sets in. The disorder is due to an excess of androgen, accompanied by an insufficiency of other hormones in the adrenals. The cortices of the adrenals are large but undifferentiated. Cortisone therapy may be of value and the local anatomy may be surgically adjusted later.

FIG. 1.—New-born baby girl, showing infantile pseudohermaphroditism.

ENDOCRINE AND CONSTITUTIONAL GROWTH DISORDERS

The growth in childhood is mainly the result of individual inherited factors and the particular hormone pattern, coupled with habits, diet and, to some extent, environment (fig. 2). Growth at puberty represents a profound impact of sex hormones on the general metabolism, with concentrated attention to bone, muscle, visceral tissues, and gonad development, with isosexual maturation. An earlier or later maturity is an individual matter, as is also the ultimate body form achieved. Physical maturity may be accelerated or decelerated by simple functional hypothalamic-pituitary action, constitutional precocity, or its converse, delay in puberty, ensuing. This may occur in several siblings and hence it is genetically conditioned. Nature will have her way and the best medical care is to leave well alone. Parental anxiety should be allayed and the child's healthy psychological state must not be disturbed. These physical maturational disorders are associated with corresponding 'bone-age' changes and early epiphysial fusions, but the 'dental age' is usually normal. All this is admirably reviewed by Jolly (1955).

TUMOURS

Tumours at the base of the brain (e.g. the so-called pinealoma), meningeal calcification after tuberculous meningitis, or hypothalamic interference after encephalitis, may, presumbly via the hypothalamic-pituitary system, disturb growth towards precocious action. Russell (1951) has described diminished general body growth in association with midbrain tumours disturbing thalamo-pituitary function in childhood. Growth changes with sexual precocity may be traceable to an œstrin-secreting ovarian granulosa-

cell tumour or to a testicular tumour prematurely secreting excessive amounts of virilizing hormones. In the male, the external genitalia may assume nearly adult proportions accompanied by a herculean build. Re-

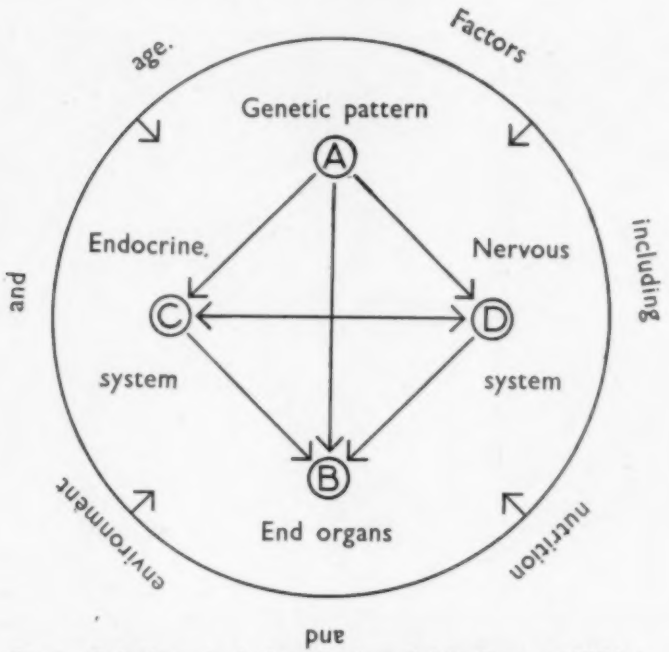

FIG. 2.—Endocrine action in the cycle of growth (after Bauer and Wilkins).

moval of such gonadal tumours may enable normal growth to be resumed. Isosexual precocity may also occur from a gonadotrophin-producing teratoma in the pelvic cavity (Levine *et al.*, 1956). Girls may develop precocious hirsutism and mammary growth (fig. 3) in association with palpable polycystic ovaries.

THE PITUITARY

The hormones of the anterior pituitary are normally responsible for the physiological velocities and spurts of growth. By longitudinal study normal variations have been ascertained (Tanner, 1955), and some facts on varieties of somatotype have thus evolved.

Pathological disturbance of growth may occur in pituitary insufficiency with infantilism, gonadal hypoplasia, delayed bone age, very slow growth, small stature, and a continued physical and emotional immaturity even into adult life—the so-called *primary pituitary infantilism*. There are no effective therapeutic pituitary extracts, but some, if minimal, improved growth and

gradual development may be effected by chorionic gonadotrophin or, later, by substitution therapy with testosterone for boys and œstrogen and methyltestosterone for girls (Wilkins, 1950). Similar growth delay may result from

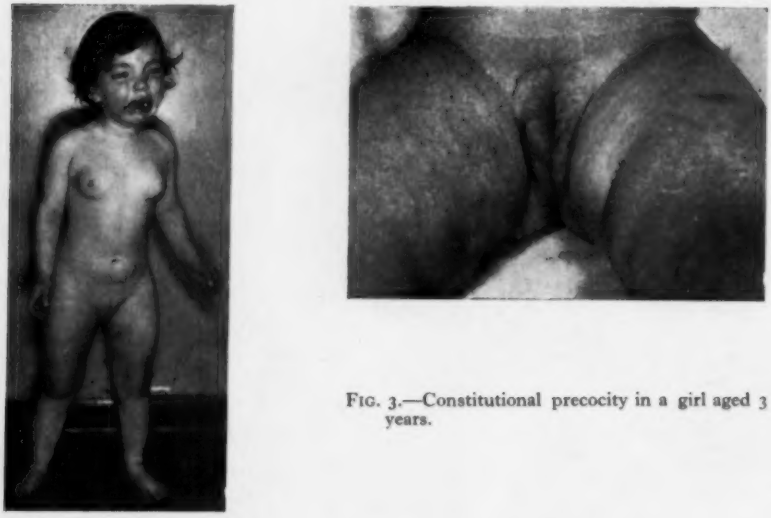

FIG. 3.—Constitutional precocity in a girl aged 3 years.

congenital cysts of the pituitary, and this may be suspected in the presence of signs of optic chiasmal pressure or local calcification demonstrated radiologically. An *eosinophil adenoma*, though rare in childhood, will initiate excessive growth before the epiphyses have united, with resulting gigantism. A *chromophobe adenoma*, which is even rarer, may cause little endocrine or general growth upset, but may cause visual and hypothalamic disturbance. A *basophil adenoma* may exist concurrently with a cortical adrenal tumour or cortical adrenal hyperplasia. Such an adrenal tumour needs urgent recognition. The clinical features (Wilkins, 1950) are characteristic: retarded growth, marked obesity, poor musculature, fatiguability, reddish striæ, polycythæmia, ruddy face, plethora, bruisability, hypertension, and hirsuitism. Special lines of therapy will be indicated according to the particular clinical pattern and the urinary ketosteroids.

Pituitary eunuchoidism.—Adequate growth hormone, or even true excess, coupled with inadequate sex hormone, causes tallness and usually thinness with hypogonadism. Substitution hormone therapy may be helpful. In *progeria*—once seen never forgotten—growth ceases early and senile features set in, including arterial degeneration and baldness. At the age of twelve the child looks like a very old person.

THE THYROID

The velocity of growth in a child is intimately concerned with optimal thyroxine production. *Cretinism* (congenital athyroidism) is a classical

FIG. 4.—The ultimate severe disordered growth in the untreated cretin.

example of impaired growth (fig. 4). From the first few weeks of life the child is dependent upon his own production of thyroxine. Every aspect of body growth and maturation is linked up with this fact. Profound changes will result from thyroid deficiency and every tissue is adversely affected in one way or another. Thus, defective general body growth will be linked with anæmia, unbalanced calcium retention and hypercholesterolæmia, and sometimes severe effects of stasis in the alimentary tract from decline of gastro-intestinal tone. The signs may appear as early as four weeks after birth (fig. 5) and the clinical diagnosis should be fully apparent at, say, three months. Bone and tissue growth and general muscular activity, as well as mental development, can be re-established to a nearly normal degree by early and regular oral thyroxine or thyroid (fig. 6a,b).

Hypothyroidism, with goitre, may be due to an inability of the thyroid gland fully to synthesize thyroxine from the lower stage of di-iodotyrosine. This *goitrous cretinism* may be familial (Hubble, 1953a; McGirr and Hutchison, 1956; Wilkins, 1954). Stunting and goitre, with general signs of a low metabolic rate, can be corrected with thyroxine, or with tri-iodothyronine (Zondek *et al.*, 1955) (fig. 7a,b). In some cases the goitre will become

markedly reduced, but in others such change may be very slow or only slight.

True *myxœdema* in childhood, usually with thyroid atrophy, may cause prolonged cessation of growth which can best be assessed radiologically by the bone-age delay and possibly epiphysial dysgenesis.

FIG. 5.—Cretinism in an infant aged 6 weeks.

There are several less classifiable types of growth disorder and delay, possibly part of a more general endocrine failure (as occurs in panhypopituitarism) rather than isolated thyroid deficiency, or where *hypothyroid dwarfism* suggests that the general tissue receptors are relatively unresponsive to thyroxine and growth is slow. In such rare cases the tissues may be more responsive to growth stimulus after giving tri-iodothyronine.

Clearly, exact diagnosis is essential to the proper care and treatment in growth disorder suspected to be of thyroid origin. Clinical facts, radiological

(a)

(b)

FIG. 6.—(a) Cretinism in a boy aged 10 weeks (four weeks after beginning of thyroid treatment). (b) Same patient as in fig. 6(a), at the age of 7 years, following regular thyroid treatment.

evidence, biochemical appraisal of plasma-bound iodine, and the iodine uptake of the gland should be ascertained. It is unwise to prescribe thyroxine, or any other iodine-containing hormone, empirically. The indi-

(a)

(b)

FIG. 7.—(a) Familial goitrous hypothyroidism due to inability to synthesize thyroxine in the thyroid gland, in a girl aged 3 years. (b) Same patient as in fig. 7(a) at the age of 5 years, showing how hypothyroidism may be corrected by thyroxine or tri-iodothyronine.

cations for its use are usually clear and limited. Primordial or genetic dwarfism, or primary skeletal delay, will be unaffected by any present known hormone treatment. The obesity of hypothyroidism is quite different in its clinical and metabolic aspects from any other form of obesity. There is no real indication for thyroid treatment in any form of obesity of childhood, except that due to hypothyroidism.

THE PARATHYROIDS

Chronic *spontaneous hypoparathyroidism* impairs general growth, giving the

child a small and plump appearance. There may be epiphysial abnormalities in the hands, lens opacities, latent or manifest tetany, and occasional fits associated with the low blood calcium. The diagnosis may be unsuspected for years. Some slow adjustment of growth may follow correction of the metabolic deficiency with dihydrotachysterol or with calciferol (Hurwitz, 1956). Some forms appear to be relatively refractory to adjustment: the so-called pseudo-hypoparathyroidism (Macgregor and Whitehead, 1954).

FIG. 8.—Congenital ovarian agenesis in a girl aged 18 years.

DIABETES MELLITUS

Insulin is now classifiable, in its several functions, as a growth-promoting hormone in childhood. It is thus in close physiological liaison with the anterior pituitary. Strangely enough, at the onset of diabetes mellitus the child is often taller than the average. The active disease, however, may soon impair growth. In fact, the favourable effects of efficient insulin treatment are reflected directly in the establishment and maintenance of a near-normal growth stream. Possibly also this ensures a more normal general state of the tissues and a lessened or delayed tendency to any consequential degenerative vascular or renal changes.

Mauriac's syndrome is indicated by hepatomegaly (from glycogen deposit and fatty infiltration), retardation of growth, obesity of the face and trunk, with secondary effects such as delayed onset of adolescence and retardation of osseous and dental development. According to Debré *et al.* (1954), it may be noted in 6 per cent. of juvenile diabetics. Diets deficient in protein are an important factor.

Hubble (1953b) notes the favourable response to an optimal protein intake and the regular use of longer acting insulin. The newer suspension insulins have the advantages of all-day action and improved anabolism and thus of avoiding wasteful nocturnal protein breakdown. Good clinical treatment should aim at a steady rate of growth with avoidance of any excessive gain in weight.

GROWTH DISORDER AND GONADAL ABNORMALITY

Pituitary eunuchoidism has already been mentioned. Extreme immaturity of sexual development is evident in ***pituitary infantilism. Delay in descent of the***

testes may be coexistent with general simple postponement of puberty. The prepuberty and puberty growth spurts are highly specific to the individual in time and degree, and may also have familial trends. The natural history

(a)

(b)

FIG. 9.—(a) Adrenal precocity in a girl aged 11 years. (b) Adrenal tumour removed from patient shown in fig. 9(a), showing early malignancy.

of the particular child should be assessed and any 'treatment' most carefully considered. Sometimes an improvement in the general nutrition of the child, especially protein, will be followed by accelerated growth and better anabolic endocrine action. A healthy general way of life is helpful. Gonadotrophic hormone or minimal amounts of œstrogen or testosterone may aid growth and general tissue improvement, but much care is necessary in this, and empirical experiment is unwarranted and may be quite unwise. Testicular dysgenesis or agenesis is usually a primordial disorder and may have to be accepted as a natural failure.

This common form must not be confused with either of the quite rare conditions of (a) *Laurence-Moon-Biedl syndrome*, in which there is an obese growth disorder, mental backwardness and genital hypoplasia, and possibly retinitis pigmentosa and polydactyly; thus including multiple effects of genetic influence on the hypothalamic-pituitary system; (b) *Fröhlich's*

syndrome of dystrophia adiposo-genitalis arising from hypothalamic and endocrine effects causing obesity, sexual infantilism with eunuchoid proportions, and diabetes insipidus.

HETEROSEXUAL OR AMBISEXUAL DEVELOPMENT

General body growth and sexual differentiation may divert in a wide variety of forms. Each affected child or adolescent needs most careful study. Anatomical confusion of masculine and feminine characters is seen in true *hermaphroditism*. Among the clinical features of *pseudohermaphroditism* are included atypical body hirsuties, clitoral enlargement or a suppressed penile anatomy; or feminization of the body with testes in the inguinal canals (this is really suppressed masculinity); or a masculine general appearance and voice and distribution of hair, with true clitoral hypertrophy associated with excess androgens from, possibly, an adrenal neoplasm. Sex reversals, or some intersexing, may be due to an ovarian or testicular tumour. Cytological tests of sex after the methods of Barr (1954) are valuable in these confusing problems, but the greatest care is necessary in the study of the patient and the cell nuclei (*Lancet*, 1956).

FIG. 10.—Obesity with 'bigness', suprapubic fat, normal genitalia and simple genu valgum, in a boy aged 7 years.

A striking example is *congenital ovarian agenesis* (fig. 8) in which body form is dwarfed, thick-set and masculine, with a short webbed neck and no secondary sexual changes at any time. The ovaries and internal genitalia are developmentally suppressed, coarctation of the aorta may be present and, strangely enough, the body cell sex nuclear pattern is often masculine in type.

Occasionally, artificial effects are produced by excess sex hormone therapy, e.g. gynæcomastia. This has also been observed during or soon after the use of chlortetracycline.

The adrenals.—Acquired hyperfunction of the adrenal cortex may be due to simple hyperplasia, a benign adenoma or a malignant neoplasm. Of Riedl's (1952) series of 22 boys, 12 had a malignant adrenal tumour. The overt signs are some accelerated growth with isosexual precocity appearing as early as one year of age and a high urinary excretion of 17-ketosteroids.

A virilizing adrenal tumour in a young girl leads to the early appearance of pubic and axillary hair and hypertrophy of the clitoris (fig. 9).

Mild or temporary premature development of sexual hair at about six years of age may be regarded as a minimal physiological variation. A feminizing tumour of the adrenal may cause gynæcomastia in the male child or adolescent. A typical Cushing's syndrome, with obesity, plethora, body and facial hypertrichosis and some signs of accelerated secondary sex characters, may be the type of growth disturbance consequent upon excess adrenal cortical secretion.

OBESITY AND THINNESS

Obesity in childhood may merely indicate a 'big edition' of human nature (fig. 10). The fatness is thus accompanied by some increase in height and arm span above the average and perhaps a tendency to simple genu valgum. The body form is often characteristic and tapering fingers may also be noted. The suprapubic fat may apparently tend to bury otherwise normal external genitalia.

In an article on *the thin child*, Dobbs (1955) gives careful and extensive consideration to the clinical aspects of disturbed growth due to causes other than endocrine. His observations and illustrations are appropriately complementary to those contained in this article.

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RECENT PROGRESS IN POLIOMYELITIS

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Publication of the 'Papers and Discussions Presented at the Third International Poliomyelitis Conference'* held in Rome in September 1954, provides an opportunity for a short review of some of the highlights of recent progress in poliomyelitis. The conference on this occasion devoted special attention to social aspects of the disease, and views were expressed from most of the 39 countries represented. Few of these countries, however, seemed to have anything like the country-wide provision for medical care, rehabilitation, and community financial help which is now available in Great Britain through the National Health Service.

TREATMENT OF THE ACUTE STAGE

Discussions on the treatment of the acute stage laid special emphasis on the need for the formation of Regional Respiration Units to deal with the grave problems associated with acute respiratory cases. In such units a coordinated team should be developed in which the anæsthetist plays a vital, but not over-ruling, part; and there should be a mobile section to assist with the transport to hospital of cases developing signs of respiratory weakness or of paralysis of swallowing. In spite of the formidable administrative difficulties involved, a few units of this kind are functioning, in part at least, in this country: e.g. in Oxford, Bristol, and certain parts of London.

The physician of the Respiration Unit should direct such a team, and, with assistants, should be prepared to render help in a patient's home in emergency. A portable equipment set should be kept in readiness for such emergencies, containing apparatus, independent of a main electrical supply, for: (1) tracheotomy, (2) intubation of the larynx, (3) suction of pharyngeal and bronchial secretions, (4) intermittent positive-pressure pulmonary ventilation with air and oxygen, and (5) postural drainage in the right and left semi-prone positions. In Bristol such a portable set includes an Oxford bellows (hand-operated), two oxygen cylinders, a Venturi sucker for attachment to an oxygen cylinder (a foot-operated sucker may be preferable), a posture frame in the form of a hinged double-inclined plane, instruments for tracheotomy, endoscopy and injections, as well as drugs, dressings, and gowns. The whole weighs 115 lb. (52 kg.) and can be transported in a small car. I am indebted to Dr. J. Macrae, Director of the Bristol Unit, for information on his experience with this apparatus on some dozen journeys

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of up to 50 miles. He has found that it is often convenient to arrange for the attendance at the patient's home of a local anæsthetist, who may be able to proceed with intubation of the larynx pending the arrival of the mobile team.

THE CARE OF PARALYSED MUSCLES

The principles underlying the care of paralysed muscles in the acute stage were outlined at the conference by Dr. Ritchie Russell. Various types of bodily fixation are still used by some, but such restrictive practices are now generally condemned. 'There is no evidence that immobility ever did a paralysed muscle any good', according to Ritchie Russell. The best way to avoid deforming postures in the acute stage is by frequent gentle passive movements and posturing of limbs and trunk by simple means, avoiding rigid fixation as by all-round plaster casts. This is combined with sedation as required. Many 'tight' muscles are simply the opponents of paralysed muscles which have been allowed to shorten a little in the acute stage. The early routine use of hot packs often serves to divert the attention of the available nursing staff from more important measures. If muscles have been allowed to become tight, however, hot packs in the post-acute stage reduce the discomfort of having them stretched.

The rate of muscle recovery should be followed by actual measurements of the strength of the muscle groups. This can be done without much difficulty for the flexors and extensors of the arm and leg by means of a spring balance. Charts showing the measured increases of strength of various muscles during a period of treatment are a valuable means of checking the efficiency of the methods employed.

A recording dynamometer, designed by Dr. E. Schuster for the Oxford Unit, measures the strength of the grip, and can be adapted to other muscle groups. It measures not only the maximum strength of a muscle group, but also the rate of fatigue developing under different conditions. A strain-gauge dynamometer for the measurement of the strength of voluntary isometric contraction, and for the training of weak muscles, was demonstrated at the conference by Dr. H. D. Darcus of the Medical Research Council's Unit for Research on Climate and Working Efficiency, University of Oxford.

THE CONVALESCENT STAGE

The convalescent stage of poliomyelitis offers a wide and increasing field of activity for the orthopædic surgeon. In all forms of rehabilitation the attitude of the patient is of prime importance. Early active vigorous treatment will usually arouse his interest and secure it for as long, at least, as there are real hopes of recovery. But treatment must not drag on for many months or for years without a definite realizable aim. Soon after the acute stage is over the patient has a right to know the real prognosis. Dr. Sedgwick Mead of the California Rehabilitation Centre writes:—

"If a muscle is totally without movement at the end of 12 weeks, its tendon reflexes absent, and its electrical response occurring only with direct current, we should tell the patient to plan to live without it. Such recovery as may occur later on will rarely be of functional importance".

Many patients can with advantage continue treatment at home after about three months in an institution.

The recently improved cuirass respirator may be of service in certain convalescent respiratory cases. It aids respiration by producing diaphragmatic motion due to alternations of pressure in the abdomen. This is insufficient in the acute stage, but is useful in weaning a patient from the 'iron lung', and in giving a few hours' daily relief from the 'iron lung' to certain permanent respiratory cripples.

PREVENTIVE ASPECTS

The achievement of natural or of artificial immunity to all three known types of poliomyelitis virus must be the general aim for the prevention of the disease. The presence of antibodies in the blood to types 1, 2 and 3 virus is the only measure of potential immunity available. This does not by any means guarantee immunity, but it is evidence of an individual's past experience of the infection; it is certainly an important mechanism for preventing poliomyelitis virus in the alimentary tract from invading the blood stream and central nervous system, and so is at least a potential safeguard against paralysis.

Dr. J. H. S. Gear of South Africa showed that the results of serum surveys for poliomyelitis antibodies in various local populations and racial groups have confirmed the conclusions reached from epidemiological studies. In areas where the people live under primitive conditions, where there is little or no sanitation, and where the drinking water is often polluted, poliomyelitis infection is hyper-endemic. In certain native communities in South Africa over 90 per cent. of the children under 6 years of age have serum antibodies against type 2 (Lansing) virus, and the majority against types 1 and 3 as well. In such communities paralytic poliomyelitis occurs rarely, almost exclusively in infants, and never in epidemics. In more advanced communities, opportunities for the spread of the virus are limited, and the age at which the majority of individuals acquire immunity is delayed as compared with that of more primitive peoples. Such communities are liable to suffer from epidemics of poliomyelitis, and the age incidence of clinical cases is higher. This trend towards epidemic paralytic poliomyelitis in older children and adults is likely to continue unless a means of actively immunizing against infection is found and made generally available.

POLIOMYELITIS VACCINATION

It is probable that vaccination against poliomyelitis will ultimately take the form of swallowing 'live attenuated vaccine' in which all three types of the virus have been made completely avirulent for man. It would be expected that in most cases these viruses would colonize the alimentary tract, and, with or without absorption into the circulation, they would certainly be excreted in the fæces. Being avirulent, they would be harmless even if absorbed into the circulation. The virus excreted in the fæces would almost certainly infect contacts, but, again, no harm would be done provided that it was completely avirulent; indeed, it would be beneficial by inducing

the formation of serum antibody. Such an ideal process can obviously only be brought about after prolonged research to produce completely stable and avirulent virus of all three types, with no possibility of reversion to the virulent state. At the present time we are barely halfway towards this goal.

Strains of all three types with greatly reduced virulence have been obtained by Sabin and others, through the method of making numerous passages of the virus in laboratory animals. Attempts by Cox to obtain avirulent virus by adapting it to grow in developing eggs have also been partially successful. Some of these strains, when injected intraspinally in monkeys, produce neither paralysis nor any detectable poliomyelitis lesions except, occasionally and irregularly, a very mild and localized paralysis. Further work in such strains may well make them potential candidates for use in human immunization. Indeed in N. Ireland, Professor G. W. A. Dick has recently undertaken a small clinical trial of such oral vaccines in volunteers. To make them more safe, they might be given in the first instance under cover of an injection of gamma globulin. But before oral vaccination is ready for general application, a prolonged period of testing in small but gradually increasing groups of volunteers will be required.

For the present the only available method of active immunization against poliomyelitis is by intramuscular injection of Salk-type formolized vaccine, in which the three types of virus, although of reduced virulence, have been killed (or inactivated) with formalin. The British-made vaccine of this type, which is now being injected into upwards of half a million British children born in the years 1947-54, is subjected to repeated safety tests, both in the laboratory where it is made and in that of the Medical Research Council, and both by means of tissue culture and by injection into cortisone-treated monkeys. Those working with this vaccine have unanimously expressed their confidence in its safety. Indeed I have seldom known in advance such unanimous assurance of negligible risk from a new biological product.

As the supply is limited, the vaccine will be given to each child chosen for vaccination, intramuscularly in 2 doses each of 1 ml., and at an interval probably of about two weeks. Samples of blood will be taken later to test for the amount of serum antibody produced. According to experience in the United States and Canada, where millions of children have been injected with a similar vaccine, 60 to 70 per cent. protection is expected against type 1 virus, and even more against types 2 and 3. How long this degree of immunity will last is unknown. In the United States there is evidence that it has lasted for the two years since 1954, when it was first given; but it is proposed there to give a booster dose about seven months after the first two injections. It is considered probable that once a reasonable titre of antibodies has been produced in any given case, immunity to some degree will remain for many years. This is borne out by a serum survey among Eskimos in the remote Barrow Village in Alaska, where evidence was found that antibodies to poliomyelitis viruses have persisted in man for 30 to 40 years in the absence of reinfection.

THE DOCTOR-PATIENT RELATIONSHIP AND 'FUNCTIONAL' ILLNESS

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SIGNS are not wanting that there has been some deterioration in the mutual trust which existed between doctors and patients before the introduction of the National Health Service. There has certainly been an increase in the number of complaints and protests by patients and relatives to executive councils, and in the number of cases brought against doctors in the Courts.

Short of these dramatic and traumatic happenings, however, it is possible that subtler forms of deterioration in the doctor-patient relationship are occurring. The tyro in general practice, and this particularly applies to busy industrial practices, soon becomes inured, though the baptism is often painful, to arguments on the telephone and degrading and exhausting wrangles at the front-door, as to whether to visit 'tonight or in the morning'. Unpleasant pressure is experienced over the issue of certificates and, indeed, also of prescriptions. Worst of all, a gnawing sense of insecurity arises in the young man as he wonders whether his older principal is fully enjoying his work or whether he is motivated, even partly, by fear. The astounding paradox is that with technique immeasurably improved, with great technological and therapeutic advances, the net result is less gratitude than formerly.

Little is left to chance nowadays—every injury of any moment (and many of no moment) is x-rayed and there must be precious few missed fractures; hæmorrhage from the bowel, if its origin be not obvious, means that the patient will have a barium enema and sigmoidoscopy before the pile ointment is prescribed. A cough that will not clear up is no longer dismissed as bronchitis until the radiologist has pronounced on the chest. When doctors could cure few ailments they were held in high regard, now in an age of therapeutic excellence they often have to defend themselves (Needles, 1954).

SOME CAUSES OF THE DETERIORATION

Needles has no doubts as to the principal cause—he lays the blame fairly and squarely on the great number of people who suffer from 'functional' illness. They constitute what he calls a reservoir of ill-will. How do they fall foul of the doctor? A common source of irritation is of course that they have too little time spent upon them. The practitioner has too many certificates to issue, too many records to keep, too many demands on his services to take a leisurely and minute interest in the neurotic and his troubles. This unfortunately also applies to the non-neurotic, and intimate knowledge of the individual is no longer always possible. In face of the extra

pressure of work practitioners are more and more tending to aggregate into groups and the patient who does not pay close attention to details of times of consultation becomes nonplussed and confused when he finds himself consulting a new and strange member of the group. It seems a pity, too, that many doctors have given up maternity work. Childbirth is a primitive event deeply charged with emotion. A confinement successfully and sympathetically managed welds mother and child and the whole family to the doctor in a way that nothing else can do. No doubt there are good reasons for leaving this task to a specialized, though of necessity somewhat impersonal, expert but human values are unquestionably lost.

Aside from these professional considerations it is evident that the advent of the National Health Service has brought about a change in emphasis. A man now tends to think of his practice as so many thousand units—an administrative measure—and there is a holistic attitude to this aggregation: for example, payment is usually made by one huge cheque four times a year. Hospital clinicians have constantly to be on guard against conveyor-belt types of arrangements for patients—a concept beloved by administrators. The individual *per se* loses importance. These are some of the ways in which the bonds are being loosened. We need to keep awake in ourselves a lively self-criticism if we are to meet the changing needs of our role.

THE CHANGING ATTITUDE OF THE PATIENT

In the third place it is undeniable that the attitude of ordinary citizens to the doctor has changed. This is not so much an isolated phenomenon in itself as a secondary result of changes in certain basic attitudes of our society. Twentieth-century man worships efficiency. Society is fast becoming a technocracy. Industry is now so big and so vast that the individual, as an individual, is quite lost. Sociologists and industrialists alike are concerned as to how to preserve human relationships in these leviathan undertakings (Ling, 1954). The inherited materialism of the last two centuries has made us concentrate too exclusively on externals, and human values have tended to disappear. Scientific and technical advances have rendered untenable centuries-old assumptions regarding the nature of the Universe, man's place and function in it, and the relation of the individual to his group. Individual unhappiness and widespread social disorder may be regarded as expressions of our disintegrating cultural traditions. In a recent survey (Frankl, 1954) it has been claimed that the spirit of our times is a collective neurosis made up of such elements as a planless day-to-day attitude to life, a fatalistic outlook ('après moi la bombe atomique'), a temptation for the individual to submerge himself into the masses, and a fatal tendency towards fanaticism. Needles quotes C. W. Mills:

> 'The uneasiness, the malaise of our time, is due to the fact that in our politics and economy, in family life and religion, in practically every sphere of our existence, the continuities of the 18th and 19th centuries have disintegrated or been destroyed, and at the same time no new knowledge for the new routines that we live and must

live has taken hold. The malaise is deep rooted, for the absence of any order of belief has left men morally defenceless as individuals and politically impotent. They have no culture to lean upon except the contents of a mass society that may shape them and seeks to manipulate them to its own ends'.

There would seem therefore to be adequate psychopathological reasons for the vast increase in the numbers of people who are functionally ill, and who seek medical advice and treatment for psychosomatic illness, psychoneuroses, and sicknesses of the personality.

NEAR-DEIFICATION OF THE DOCTOR

In short, as a famous psychiatrist has said, Western man turned away from the priest to the doctor, someone who seemed to be more efficient, more practical, someone who seemed to incorporate the admired and worshipped science and devoted it to that most attractive goal, the perfection of human health and the alleviation of human suffering—*soluti et solatio ægrorum*. But the emphasis soon canalized exclusively on health; solace was not greatly in demand. Now this near-deification of the doctor I take to be a fourth cause of our difficulties for it has some not unexpected results. We had a good run. For a long time we have been good 'copy'. Medical journalism has flourished. Many best sellers, films and plays have been written about us. In a recent survey by questionnaire it emerged that the career which most parents in this country would choose for their sons would be a career in medicine and we are familiar with the vast over-application for places in medical schools which has been the rule in post-war years. Now the inevitable disenchantment is taking place before our very eyes. How could we hope to maintain our inflated pre-eminence? The age of technology and sub-human machine-like efficiency was bound to become dissatisfied with a science so incomplete, so fallible as medicine, and the keenest and most vociferous disappointment is felt by those who try us at our weakest point—the sufferers from psychosomatic and 'functional' illness. Reliable observers estimate (Balint, 1954) that of all attendances at surgeries and clinics, anything from 25 to 50 per cent. are not suffering from any demonstrable pathological entity or nosological syndrome. If in applying our somatic remedies, we fail them, we need not wonder that they, having been led to expect so much, constitute in their chagrin a large reservoir of cynicism and ill-will against which we have to defend ourselves.

IS THE RELATIONSHIP WORTH PRESERVING?

If we feel therefore that our relationship with our patients has deteriorated, and if we know or can guess at some of the reasons for this state of affairs, then clearly we must ask ourselves whether we shall attempt to arrest or reverse the process, whether indeed the relationship has anything of value that is worth preserving. In the days when it was fashionable to regard medicine as an art as well as a science, physicians had no doubt that the doctor-patient relationship had value, both in therapeutic outcome and in

human terms. It has hitherto always been recognized that this fact accounted for much of the best that was to be had in the medical life. Here lay much of the doctor's satisfaction in his work. It is noteworthy that in the least scientific branch of medicine, namely psychiatry (the branch most germane to 'functional' illness, incidentally), the whole secret of the therapeutic process is believed to be locked up in this very human relationship: e.g. the transference beloved of the Freudian with all its fanciful and symbolical appurtenances. But the impact of sociology and anthropology and the increasing influence of Sullivan and the Washington school of psychiatry are making us familiar with the more forthright term—interpersonal relationships. There is no suggestion that the psychological understanding need always be very profound or complex. As an example of what is meant, Ozani (1954) may be quoted:—

'There is a point at which the values of democracy, religion and medicine agree —the value and dignity of the individual, the value of human understanding and kindly relationships with and assistance to another person who must himself continue his unremitting struggle to find an adjustment and meaning in his life'.

This perhaps puts the matter rather too strongly and over-emotionally to suit our insular restraint.

Yet it is almost impossible to keep emotion out of the picture. Who has not knocked at the door of a sick person and been welcomed in with visible relief and diminution of tension before anything was done at all? Who has not been told at some time: 'I felt better as soon as I saw your face'? Whether this be sympathetic magic or no, it seems to be an integral part of medical practice: a *sine qua non* of the good doctor. Gowers once said 'If every drug in the world were abolished the physician would still be a useful member of society'. Needles recalls Houston's teaching that the doctor himself is a potent therapeutic agent. So long therefore as 25 to 50 per cent. of the work in general practice consists of treating neurosis and functional illness—and there seems little indication that the numbers will diminish—the inference must be that the doctor-patient relationship should be retained as vigorously as possible, for on it does therapy depend. Two viewpoints from different quarters may be adumbrated in support:—

Balint (1954) is of the opinion that, although it is true that establishing and maintaining a proper therapeutic relationship needs much more time than prescribing a bottle of medicine, in the long run it can lead in many cases to a considerable saving of time, for both the doctor and his patient. This might be taken as a representative present-day psychiatric view. Speaking as a general practitioner, however, Pinsent (1951) describes how he deals with 40 to 50 per cent. of all his consultations in a busy industrial practice. These patients receive no medication, they are treated purely by advice and health education, their symptoms explained and worries put at rest. On the whole the replacement of medicine by advice was well accepted, few patients were 'lost', and Pinsent considers this a return to the classical concept, etymologically sound at least, of the doctor as an adviser and teacher to his patients.

THE INDIVIDUAL NEUROSES

In an attempt at reform there would seem to be two main lines of approach: the individual and the collective.

If 'functional' illness, or most hazardous of all, 'functional' overlay on top of somatic illness, is the main reason for poor relationships between doctors and patients, need we go on treating it in quite the resigned fashion that we have been doing? The contribution that we can make here has been well mapped out in some recent articles which are reassuringly unanimous in their directives. Bennet (1953) is directly encouraging when he indicates that techniques are of less importance in this particular situation than in any other branch of medicine. He reiterates the view that in the relation between patient and doctor lie the essentials of cure or improvement. (In passing it might be emphasized to the patient that improvement is what is being aimed at; 'cure' is fortuitous, even unlikely). As well as having an understanding and sympathetic attitude, and displaying a sincere and friendly interest, however, an appreciable degree of detachment should be maintained. Batchelor (1953), too, emphasizes that the attitude of the doctor is all-important: not censorious and, equally so, not too kind, or he will bring about undue emotional dependence on himself which becomes intolerable, and may actually hinder the patient's improvement.

Another factor which gives many practitioners qualms before leaving the beaten track of somatic medicine is that they feel that they have had inadequate instruction in psychological medicine. But, as just stated, success depends less upon the practitioner's theoretical principles than on his personality, the direction of his interests and his insight—the word has no magical connotation, anyone can have some degree of it, given sympathy, empathy and intuition.

Even though half an hour spent in talking with the patient (not to the patient) can actually be at once therapeutic and time saving, many will feel that these considerations are unrealistic while practices remain at their present size and pressure of work continues. If the point of view put forward here is accepted, it follows that many present-day practices are too large for the exercise of these skills. It is disquieting to note that the profession is now officially concerned at the prospect of the medical schools producing too many doctors in the next few decades. No doubt, since the cost of the Health Service is likely to remain as static as successive governments can maintain it, there is reluctance to welcome more colleagues into practice, since it will mean a progressively smaller share all round. This is a very human and understandable feeling. In addition there is the further chance that, having become used to large numbers of patients, we have also become accustomed to the superficial type of relationship which this entails, and in fact we may now be afraid of anything more profound.

Wittkower and White (1954) put the matter plainly. Doctors should step down from the near divine role and give up the pose of omnipotence and omniscience. We ought to feel secure enough to admit our limitations and cease from reaching out for and taking on tasks beyond our capacities. 'But we also have to live and support our families, and the temptation is often great to place self-interest before the interest of the patient, to promise "miracle" cures against better judgment, to

prescribe injections which are not needed or to play up to the patients' demands for gadgets which may not be required'.

Not only could there be a great saving in time, money and effort (and the patient's happiness) if psychosomatic patients would not again and again be referred for specialist examinations and elaborate laboratory tests, but we should also prevent a good deal of neurosis from becoming permanent or passing over into psychosis. Overemphasis of the symptoms in this way leads to iatrogenic or doctor-caused illness—one of the psychiatrist's intractable problems. The practice of medicine consists not only in the application of biological knowledge, but also in the exercise of considerable degrees of social and psychological understanding.

THE COLLECTIVE NEUROSIS

If we believe that the collective neurosis is primarily a sickness of the community and society, we need not be afraid to say that medicine can only deal with part of the problem, and that the over-all solution lies in other spheres. It is a folly to claim to do more than we can. Psychosomatic medicine is not yet established in its own right. It is practised almost exclusively by psychoanalysts and, although interesting speculations abound, one has to confess that so far, empirically speaking, they are barren. Not everyone will agree to consult a psychiatrist. It is doubtful if this is desirable even if it were feasible. The problem is one for society as a whole and, although politics have made medicine their business, there is no obligation upon us to pour millions of gallons of medicine down our patients' throats as a kind of twentieth-century *panem et circenses*. With the best will in the world, whatever therapy we use, it seems likely that results will be something less than satisfactory and, as is now happening, we shall be held responsible for the failure. The problem is not ours alone, it is not even the exclusive property of the Welfare State or the National Health Service, although it probably exists more acutely here; litigation against doctors flourishes also in North America.

We need not be ashamed to admit the limitations of our capabilities. Socrates was always saying that he knew nothing, and truth of intercourse was sound ethics long before economic expediency demanded that the customer be always right. To say all this is not to absolve us from the duty of continuing to try to help patients in their difficulties; but the extent to which we have recourse to placebos is a measure of our insecurity. When the nature of our daily work is such as to expose us to varying degrees of unpleasant pressures, there is then a special danger that standards will be lowered (Lewis and Maude, 1952).

But, even if the problem is at bottom a sociological one, we as a group are involved in society, and society looks to us to point the way out of the difficulty. As is so often the case, the main hope lies in prophylaxis. Public health is beginning to accept mental hygiene as its proper concern (M'Lennan and Small, 1955), although, as always in breaking new ground, progress

is slow and often stumbling. There is sometimes a feeling among practitioners that patients often approach their problems in a wrong-headed way and cannot be made to see reason. Having been led to expect that popular education, ideally at least, would create a well-informed, stable and contented society, we are disappointed with the results. But that may not be the fault of education itself, so much as the way it is applied (*Lancet*, 1955). For example, the Socratic method of group discussion has been reintroduced of late years, with some success, into psychotherapy and now shows signs of becoming an increasingly important instrument of learning in schools, universities and many other walks of life. The usefulness and applications of the method are described in a recent symposium published by the Central Council for Health Education (1954). Any method which encourages growth and development of the personality, with special reference to powers of self-expression and self-objectification, is a safeguard against ennui and the sense of frustration.

Here then are two spheres of activity where we can use the full weight of our influence, even though the results will not be appreciable for many years. Public health ventures into mental hygiene deserve our support and encouragement. We cannot expect to have a voice in general education programmes, but we can go on saying that the collective neurosis will only diminish when individuals are educated to accept responsibility. The developments and researches in medicine and sociology call for a re-examination of frontiers (Roth, 1956).

SUMMARY

A deterioration of the doctor-patient relationship is postulated in the light of certain present-day facts.

Some reasons for the decline have been suggested by reference to changing conditions of practice. A powerful factor is believed to be the great increase in the amount of 'functional' illness, which is itself a product of altered values in the social and cultural life of the community.

Evidence is presented that the doctor-patient relationship is therapeutically valuable, and certain suggestions are made for its preservation.

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SOME EARLY COLLECTIVE INVESTIGATIONS

A CHAPTER IN THE HISTORY OF MEDICAL RESEARCH

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Mass observation of the pattern of disease and of the effects of treatment has come again into prominence through the work of the College of General Practitioners. The potential value of such investigations is undeniable and during the last two hundred years many attempts at research of this nature have been made. This article traces the history of these earlier investigations.

The use of experiment and observation in the pursuit of scientific truth dates from the writings of Bacon. In his *Novum Organum* he described his idea of a learned society staffed with a hierarchy of scientists, among which were to be the Merchants of Light who bring news from foreign lands, the Depredators who ransack books for scientific facts, the Mystery men who collect experiments in the mechanical arts, the Pioneers who try new experiments, the Compilers who tabulate the results, the Dowerymen who try to derive practical benefit, the Lamps who direct new experiments, the Inoculators who try these, the Interpretors of Nature who 'raise . . . discoveries into greater observation, axioms, aphorisms'. He called for the collection of 'histories' on every conceivable subject, and such histories as he pictured could only be collected by united effort. The compilation of the 'histories' became for many decades the ideal of the study of nature.

Descartes put the matter concisely when he wrote:

> 'As to medicine, all that men know is almost nothing in comparison with what remains to be known. . . .I [decided] to beg all well inclined persons to proceed further by contributing . . . to experiments and communicating them to the public . . . in order that the last should commence where the preceding had left off and thus by joining together the lives and labours of many, we should collectively proceed much further than any one in particular could succeed in doing'.

JOHN FOTHERGILL AND THE 1775 INFLUENZA EPIDEMIC

On August 11, 1767, William Heberden read to the College of Physicians a short paper on the 'epidemical cold' of June and July of that year. In his concluding remarks he said: 'As the same disease was reported to be common about the same time in many other parts of England, and more fatal than it was in London, it is very desirable that the Physicians of those places would favour the College with what they observed relating to its history and cure'. There is no evidence that this suggestion was taken up with regard to the epidemic of 1767, but in 1775, when a further influenza epidemic swept the country, John Fothergill drew up 'a sketch of the epidemic disease which appeared in London towards the end of the year 1775' and

circulated it to his friends in all parts of the country. The sketch, which was a four-page document, gives a succinct account of the epidemic as seen by Fothergill. The disease, we are told, first attacked most of the servants and sometimes others in many families in London.

'They have colds, coughs, sore throats and various other complaints. . . . In the space of a week these complaints became more general; few of the servants escaped them, especially the men who were most abroad; many of the other sex, likewise, and people of higher condition, were attacked, nor were children exempted. . . . The disease, which had hitherto been either left entirely to itself or had been treated with the usual domestic medicine appropriate to colds, now claimed the attention of the Faculty and for the space of three weeks kept them for the most part universally employed. . . . Most of those whom I saw were seized (and often so suddenly as to be sensible of the attack) with a swimming or slight pain in the head, soreness of the throat, and all over the body with a sense of coldness, particularly in their extremities. A cough soon followed, a running of the nose, watery eyes, slight nausea, frequent calls to make water and some were seized with diarrhœa. . . . More or less of feverish heat, unquietude, pain about the breast and in the limbs soon succeeded but in various degrees. Many were capable of continuing in their usual occupations under these symptoms, others were obliged to submit to confinement, not a few to their beds'.

This description could scarcely be bettered today. Fothergill concluded:

'If those Physicians in the Country, into whose hands this essay may come, will be so obliging as to mention the time when this epidemic made its appearance in their neighbourhood, and where it differed from the preceding Sketch, either in the symptoms or the method of cure, they will likewise contribute to the same good purpose. The united observation of the Faculty at large must greatly exceed the utmost efforts of the individual however warmly he may be disposed to promote the utility of his profession'.

The replies received were printed along with the sketch. The first is from Sir John Pringle, who described his own symptoms and remarked that he had no cough. He concluded that 'such epidemics (of which there have been four in my remembrance) do not depend on any principles we are yet acquainted with but upon some others, to be investigated, and by such means as Dr. Fothergill very properly and most commendably proposes to be done by the united inquiries of his brethren'. Other replies were received from Dr. Heberden, Sir George Baker, Dr. Henry Revell Reynolds, Dr. William Cumming of Dorchester, Dr. Thomas Glass of Exeter, Dr. Ash of Birmingham, Dr. W. White of York, Dr. Heygarth of Chester, Dr. R. Pulteney of Blandford, Dr. William Thompson of Worcester, Dr. D. Skene of Aberdeen and Dr. Campbell of Lancaster. Glass of Exeter describes the devastation which occurred in the Devon and Exeter Hospital when 162 servants and patients were all coughing together. Replies were also received from Drs. Webber of Hull, Thomas Percival of Manchester and J. Coakley Lettsom of London, but for reasons of space their observations were not published.

THE 1782 INFLUENZA EPIDEMIC

The number of replies that Fothergill was able to obtain is an indication of the desire among physicians of that period to share their experiences. The rise of voluntary hospitals in the mid-eighteenth century was a big stimulus to this end. The Royal Society, through its proceedings, played a

large part in the propagation of medical knowledge, as also did such journals as the *Gentleman's Magazine*, in which many interesting clinical reports were published. The last quarter of the century saw the foundation of numerous medical societies. It is not surprising therefore that when the next epidemic occurred in 1782, we find collective reports published by the Royal College of Physicians and by the Society for Promoting Medical Knowledge.

The account of the Royal College of Physicians (1785) describes the progress of the disease from Newcastle upon Tyne in the north, through Norwich and Bury St. Edmunds, to Kingston and Guildford in Surrey. Its spread is traced northwards to Edinburgh and Glasgow and later to York and Liverpool. Its appearance is noted in Plymouth and the western districts of Cornwall. It was observed to attack the fleet and transports in various ports. A good clinical description is extracted from the reports and treatment is considered. The bills of mortality for London are provided. From the number of places mentioned it is obvious that fairly numerous reports were collected and analysed by the College.

The Society for Promoting Medical Knowledge was founded in 1782 by Samuel Foart Simmons, who seceded from the Medical Society of London two years after having held the post of President (Fox, 1919a). With Drs. Edward Gray and Edward Ford, he formed 'a Society for Promoting Medical Knowledge by collecting and publishing such papers on medical subjects as they think worthy of being preserved'.

In the library of the Royal Society of Medicine is an unsigned letter written to Dr. Lettsom at Grove Hill, possibly from Simmons. From this letter, which introduces the proposal to form a 'Society for the Improvement of Medical Knowledge', we are reminded of the feud which existed between the Fellows of the College and the Licentiates. At that time it was necessary for those wishing to practice in London, or within seven miles of its centre, to hold the licence of the College. But the College, whilst granting its licence freely, restricted its Fellowship to graduates of the Universities of Oxford and Cambridge—universities which made no effort to teach the practical side of the subject in which they granted degrees. Many men wishing to practise medicine were therefore constrained to go over the border to Edinburgh or Glasgow or over the Channel to Leyden where the teaching was more efficient. The anomalous position arose where many of the leaders of the profession, men of the standing of Fothergill and Lettsom, for instance, were unable to take part in the affairs of the College. So aggrieved were the Licentiates by this that on one occasion, with the help of a locksmith to open the gates, they forced an entry to a comitia of the College. In 1772, and on several previous occasions, lawsuits had been taken out by the Licentiates with the object of gaining the rights of Fellowship. The title of the manuscript on the constitution of the Society proposed by Simmons reads: 'Notes on The Society of Physicians of London Instituted for the Improvement of Medical Knowledge and also for building a new College of Physicians'. There was a move afoot to form a rival body; in

its proposed constitution the new society was to have a president, censors and a treasurer and was to hold quarterly general meetings and an annual dinner (Fox, 1919b). It is interesting to conjecture that this proposed new foundation of Licentiates might have become a College of General Practitioners!

The first publication of the Society was an inquiry into the influenza epidemic, carried out on lines parallel to that embarked upon by the College. The *London Medical Journal* (1783), edited by Simmons, gives notice of the Society and adds a paragraph:

> 'An account of the late influenza is expected from the Royal College of Physicians in London. An address from their Registrar (Dr. Reynolds) to the Physicians of Great Britain and Ireland, has appeared in several public prints, requesting them to communicate to him the results of their observations on this subject. The Society instituted for the improvement of medical knowledge, a part of whose plan it is to compile an accurate register of epidemical diseases, are likewise collecting materials for a similar history'.

Compiled by Dr. Edward Gray, the report (Gray, 1784) is in narrative form and is supported by copious extracts from thirty-five correspondents set out in footnotes substantiating each statement made. This is probably the first successful attempt at collective investigation. The report is quite masterly. The marshalling of the evidence on the manner in which the disease was produced and propagated has quite a modern ring. Some physicians, we learn, thought it was due solely to the state of the weather. Others thought the cause was conveyed by and resided in the air. The majority 'concurred in the opinion that the influenza was contagious, in the common acceptation of the word, that is to say, that it was conveyed and propagated by the contact, or at least by the sufficiently near approach, of infected persons'. Instances are cited of its occurrence on ships after they had been boarded by customs house men. The spread of the disease from town to town is traced: 'thus, for instance, it was at Dartmouth much sooner than at Tinmouth, though the last mentioned place is situated between Dartmouth and Exeter'; if it had been due to a state of the air, it should have struck all three places simultaneously. This epidemic was known as Russian influenza. The quotations made from the reports of the participating physicians bear abundant evidence of the powers of observation and high standard of learning among the profession at that time.

Influenza was a frequent visitor during the last quarter of the eighteenth century. The next major epidemic occurred in 1788 and Samuel Foart Simmons, the editor of the *London Medical Journal*, wrote a report of the epidemic based on his own observations in the Westminster Dispensary (where he treated 160 cases), and on reports of correspondents from all over the country.

BEDDOES AND THE 1803 INFLUENZA EPIDEMIC

After a lull of fifteen years the disease broke out again in 1803. This time it was the subject of two inquiries: one by Thomas Beddoes of Bristol and the other by the London Medical Society. Thomas Beddoes (1760-1808),

the father of the poet, Thomas Lovell Beddoes, and the friend and patron of Humphry Davy, was one of those great individualists whom the study of medicine is so likely to produce. Educated in London and Edinburgh, he obtained his M.D. at Oxford where he became reader in Chemistry in 1788. In spite of attracting, according to his own statement, the largest classes that had assembled in the University since the thirteenth century, he resigned his post in 1792 on account of his sympathy with the French Revolution. He then set up in practice in Bristol and founded a Pneumatic Institute for the treatment of disease by inhalation. It was while working in this Institute, which was financed by Wedgewood and equipped with apparatus constructed by Watt, that the boy Davy discovered the properties of nitrous oxide in 1799. Davy, when he first met Beddoes, described him as 'uncommonly short and fat, with little elegance of manners' (Thorpe, 1896).

In making his inquiry Beddoes asked five questions of his colleagues:—

(1) When did the influenza appear and disappear with you?

(2) Was its date different in remote places within your reach?

(3) After being general, did it occur for some time in single instances?

(4) Did it ever seem to pass from person to person?

(5) If so, is it likely that clothes or fomites conveyed it in any case?

He received 124 replies from doctors all over the country and their reports were published in the *Medical and Physical Journal* (1803). A summary was promised but was never published.

THE POSTMASTER-GENERAL COOPERATES

The second inquiry into the 1803 epidemic was undertaken by the Medical Society of London which sent a circular letter to its members requesting the answers to certain questions. The letter ran:

'The Medical Society of London, of which you are a corresponding member, convinced that every Medical Practitioner will consider the late epidemical disorder, commonly termed the influenza, as an object peculiarly worthy of investigation, and wishing to collect for publication a complete history of this disease, earnestly request your answer to all or any of the subjoined questions'.

There followed 32 questions. The first four are concerned with the date of appearance and disappearance of the disease and the time of maximum incidence. The next six seek information on the symptoms, fatality rate, age, sex, and occupational incidence. Then follow questions on treatment, and question 12 specifically asks: 'What effects followed bleeding, general or local, emetics, purgation, opiates, sudorifics, blisters or other remedies . . .' The sufferers from influenza in those days did not easily succumb! Questions concerning convalescence and relapses come next. The last ten questions were designed to determine its infectivity by collecting observations of contacts, its occurrence in closed communities, the effect on its spread of wind and weather and its passage from place to place. The questionnaire concluded:

'The Society being desirous to ascertain whether the epidemic be contagious or not, and to collect such meteorological observations as will throw light on the

natural as well as the medical history of the disease, particularly request your attention to these objects'.

This investigation is noteworthy in that it is the first recorded instance of State help in a collective investigation. The letter ends:

'Their Lordships the Post Master General on an application made to them, considering it as a matter interesting to the community, and in the hope of the information obtained proving eventually of benefit to the human race, have, with the utmost liberality, consented that the correspondence upon the specified objects of the foregoing queries shall be carried on free of expense, provided that the replies to them be sent addressed to the Medical Society of London; in letters not sealed, under cover to Francis Freely Esq., London'.

Fifty-eight replies of varying length were received and published, but, as with Beddoes' inquiry, no effort was made to tabulate or summarize them, so that the value of the work was vitiated to a great extent (Memoirs of the Medical Society of London, 1805).

SMALLPOX IN NORFOLK AND CHICHESTER

In 1819, Norfolk suffered a severe epidemic of smallpox, and Dr. John Green Crosse, a practitioner of that city, set on foot an inquiry to find out the effect of vaccination on the incidence and severity of the disease. In his book (1820) he reported on 200 cases which occurred in 112 different families comprising 603 persons; 91 of these had been vaccinated and all except two escaped the disease. To gain a more complete picture he circularized most of the practitioners in Norfolk and the adjoining parts of Suffolk asking them 12 questions arranged under three headings:—

(1) Concerning the practice of vaccination.

(2) The recent prevalence of smallpox.

(3) The effect which the contagion produced.

Of the 93 doctors who replied, two had never vaccinated any individual; the remaining 91 were able to state that they had vaccinated 120,000 people, and 78 of them reported that they had seen no deaths from smallpox after vaccination. Six were less emphatic or more general in their answers. Forty-four had never seen smallpox after vaccination and eight had never seen it after vaccination which they had pronounced complete. Three had never seen it but had known of cases in which varicella had been confused with smallpox. Of those who had seen smallpox after vaccination, 23, who specified the number of cases, had seen 81 cases between them, 40 others had seen some mild cases.

This survey is interesting. It shows not only the success of vaccination, but also the large proportion of general practitioners who were offering vaccination to their patients 21 years after the publication of Jenner's work. The extent to which the population were in the habit of receiving medical attention may be gauged by the statement that 28 surgeons together had 593 smallpox cases with 97 deaths; yet, in addition, in their districts there had been 180 deaths from the same disease in families unvisited by them.

At Norwich, in 1812, Dr. Rigley had started a far-seeing experiment in preventive medicine when he persuaded the Board of Guardians to offer

half-a-crown to parents for each child brought to be vaccinated. This undoubtedly increased the number of persons protected.

From an account of the epidemic at Chichester in 1822 we get an idea of the prevalence of lay inoculators. John Forbes, in recording the epidemic, collected information from 19 surgeons in the district. He complains that the Overseers of the Poor called upon 'a common farmer, of the name of Pearce' to inoculate for them. Pearce, who claimed that he never got more than 20 vesicles from his operation, received half-a-crown from each case.

> He inoculated upwards of a thousand and this record, 'and the substantial honours attendant, were too tempting to the vulgar cupidity to be left unshared, and, accordingly raised úp no less than three formidable rivals of his own sex, besides many sly poachers of the other. These men (a knife-grinder, a fishmonger, and a white-smith) spread themselves over the country and, partly by undercharging, and partly by the vacuities of visitation occasioned by the great practice of Pearce continued to glean a plentiful harvest after him'.

Forbes (1822) tried to ascertain whether cowpox vaccination was more successful than the old inoculation. His results showed little difference between the two methods.

CONCLUSION

When the expense and slowness of the postal service and the absence of shorthand-typists are remembered, one must admire the industry which enabled these early research workers to achieve such remarkable results.

These investigations were the beginning of a method of research which became common during the nineteenth century when it was encouraged by the Provincial Medical (later British Medical) Association and which has been continued spasmodically ever since. Today, with our rapid postal service, and all the blessings of modern secretarial assistance, there should be no difficulty in obtaining valuable information on any suitable problem, provided the initial work has been well planned.

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GENERAL PRACTITIONERS' FORUM

TINEA PEDIS IN GENERAL PRACTICE

By W. GOULD, M.B., B.Ch.,
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From the point of view of the general practitioner the major problem of tinea pedis is that of relapses which are notoriously common, due to recurrence or reinfection, particularly following a period of hot weather.

SCOPE OF OUR INVESTIGATION

In the majority of cases it is possible to achieve temporary remission of the condition by the application of one of the numerous fungicidal agents now available, but the primary objective of the trial which we have undertaken was to evolve a simple form of treatment that could readily be carried out by the patients themselves and which would afford permanent relief, even during the summer months. This would not only benefit the patients themselves, but would also reduce the number of visits to the doctor's surgery—an important consideration under present conditions.

The difficulties encountered in attempting a controlled clinical study of any fungicidal agent were discussed by Goldman and his associates (1943). Regular microscopical or cultural mycological examinations of specimens from individual patients are virtually impossible in a busy general practice. We therefore wish to emphasize that in this investigation diagnosis of the disease and its progress during treatment were deliberately based solely upon clinical inspection and the relief afforded to each patient.

A further complication of tinea pedis is the possibility of secondary bacterial infection and, as no bacteriological or mycological examinations were undertaken, we felt that an agent with both bactericidal and fungicidal activity would be advantageous. Of the products considered for trial, our attention was drawn to the organic compounds of mercury which are effective against both pathogenic bacteria and fungi.

MacKenna (1948) noted that among fungicides, the mercurials, especially the phenylmercuric compounds, have attracted much attention. Levine (1933) cured all of 110 patients of tinea of the feet using a lotion and ointment of phenylmercuric nitrate and it was effective where other standard medicaments had failed. Similarly, Goldman *et al.* (1943) treated 114 cases of tinea pedis with a cream, ointment, solution and tincture of phenylmercuric borate and nitrate and confirmed that they were active fungicides and that irritation was produced in only about 2 per cent. of the cases treated.

As the question of relapse was our prime consideration, we were interested to read that Bushby and Stewart (1949), after investigating a large number of antifungal substances, concluded that it would appear that high *in vitro*

activity of a substance provides little indication of its possible *in vivo* activity and that a capacity to penetrate through the skin is indispensable to maximum therapeutic efficiency. Because of this we selected for trial a colloidal salt of phenylmercuric hydroxide, namely, phenylmercuric di-naphthylmethane disulphonate ('penotrane'). This compound was shown by Goldberg *et al.* (1950) to possess potent bactericidal and antimycotic activity coupled with deeply penetrative properties through the living skin, effective concentrations being produced at a depth of 2 mm. below the surface of the skin. It was also shown that this compound does not cause any significant biochemical change in living tissues. It was hoped that by building up significant bactericidal and fungicidal tissue concentrations of this compound by virtue of its substantivity to protein, the incidence of relapses would be reduced.

METHOD OF TREATMENT

'Penotrane' is available in the form of an aqueous solution (0.1 per cent.), a jelly (0.1 per cent.), a tincture (0.1 per cent.) containing 50 per cent alcohol, and a dusting powder (0.4 per cent.).

Results	No. of patients	Percentage of patients
Very good	17	38%
Good	19	42%
Fair	7	15.5%
Poor or no result	2	4.5%

TABLE 1.—Results of treatment in 45 patients with tinea pedis.

The patients were instructed to observe strict foot hygiene: twice-daily foot washing with separate towels, avoiding contact of bathroom floors and mats with bare feet, together with daily changing and washing of their socks. The powder was used throughout treatment by dusting on to the feet and into the socks and shoes. Twice-daily applications, morning and night, of either the solution, jelly or tincture, were carried out. The jelly was applied with gentle massage; the solution and tincture were applied with swabs of cotton-wool and allowed to dry before dusting the feet with the powder. In most cases the solution was used initially with the powder, as evaporation of the lotion assisted in drying and hardening any sodden white skin. If continued applications of the solution tended to produce excessive drying, treatment was replaced by applications of the emollient jelly to prevent the skin from becoming brittle and scaly, but the solution was again applied at the first sign of any renewed sogginess.

RESULTS

Forty-five patients were included in our investigation, and the results are shown in table 1. In addition, a further two patients were treated but one died from other causes and the other left the district after showing considerable improvement.

The results were classified as 'very good' when all lesions were healed clinically and the patients reported complete absence of discomfort. 'Good' results were reported in those patients in whom healing was complete clinically but there was some discomfort (e.g. mild irritation but no obvious lesions), particularly in hot weather—this was usually controlled by further applications of the dusting powder. 'Fair' results were those patients who experienced considerable relief from irritation but whose lesions were controlled but not healed.

Duration of tinea before treatment	Duration of treatment			
	1-3 months	4-6 months	7-12 months	Over 12 months
Less than 1 year	12 (86%)	2 (14%)	—	—
1 to 3 years	12 (50%)	5 (21%)	7 (29%)	—
More than 3 years	—	2	1	3

TABLE II.—Duration of treatment in relation to duration of disease in 44 cases of tinea pedis.

In one case in which the result was classed as 'poor', little relief was experienced and in the other there was no response whatsoever to the treatment. It is possible that in the absence of mycological examinations, these two cases were not diagnosed correctly.

DISCUSSION

The first patient began treatment in May 1954 and the last one in March 1955. All patients except four completed treatment by, or before, May 1955. The duration of the disease before treatment varied from two months to 11 years; it was less than a year in 14, from one to three years in 24, and more than three years in six. The period of treatment varied considerably and, as is shown in table II, in most cases was related to the duration of the disease preceding the initiation of treatment. The most significant point which resulted from this trial was that not one of the patients who had successfully completed treatment by, or before, May 1955 reported any recurrence of the disease throughout the summer of 1955.

Applications of an aqueous solution, particularly in the initial stages when the tissues were moist, produced the most rapid results and the greatest degree of relief to the patient. In the four cases in which the tincture was applied, an exacerbation of symptoms was produced in every case, and it was therefore decided that the use of this preparation should be given up. Whilst applications of the jelly prevented the skin from becoming brittle and scaly, in some cases its prolonged use tended to produce renewed sogginess of the tissues which was rapidly controlled by reverting to the aqueous solution. Most patients reported relief of irritation and of burning of the feet from the continued use of the dusting powder throughout treatment.

Except in the case of those patients who experienced an exacerbation following applications of the tincture, no untoward or toxic effects were

reported, in spite of the fact that in three cases treatment was continued for one year.

SUMMARY

(1) A trial was undertaken to evolve and evaluate, entirely on clinical inspection, a method of treating tinea pedis in general practice which would result in reducing the incidence of relapses.

(2) Of 45 cases treated with preparations of phenylmercuric dinaphthylmethane disulphonate ('penotrane'), good or very good results were obtained in 80 per cent., fair results in 15.5 per cent. and poor or no result in 4.5 per cent.

(3) There were no reports of relapse throughout the summer in any of the patients who had successfully completed treatment by, or before, May 1955.

(4) The most rapid results and maximum relief were obtained by applications of an aqueous solution combined with the use of a dusting powder.

The material used in these trials was supplied by Ward, Blenkinsop & Co. Ltd.

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THE TREATMENT OF IMPETIGO

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In a preliminary report (McMaster, 1955) reference was made to the satisfactory treatment of 30 cases of impetigo by means of 'graneodin' ointment, each gramme of which contains 2.5 mg. of neomycin and 0.25 mg. of gramicidin. Since this report was presented, the trial has been extended to embrace 57 cases and particular attention has been paid to the possible development of sensitization and resistance. The majority of cases were of the type usually described as staphylococcal impetigo, with either thin or absent crusts, many of the lesions being circinate.

Neomycin has been said (Waisbren, 1956) to have 'the widest antibacterial spectrum of any of the antibiotics' and it is highly active against many gram-positive and gram-negative bacteria. Its effects on streptococci and pneumococci, however, are less impressive and the addition of gramicidin is advantageous because this antibiotic enhances the activity of neomycin *in vitro* against such gram-positive organisms (Heseltine, 1955). There have been many warnings against the topical use of antibiotics which are administered systemically, because of the dangers of resistance and sensi-

tization. Neomycin is rarely given systemically and gramicidin is never used in this way.

RESULTS OF TREATMENT

Of the 57 patients with impetigo treated by means of 'graneodin' ointment, 54 were infants and children. There was no selection of cases. Over a period of sixteen months in general practice, every child with impetigo was treated, irrespective of the length of time the lesions had been present when first seen. When crusts were present, the removal of these was advised before medication. The ointment was rubbed well into the affected areas three times daily and in the case of very young children the lesions were covered with gauze. No other medicament was used. Complete clearance of the infection was observed within three to seven days. There was no evidence of sensitization, and in each case the organism was obviously sensitive to the neomycin-gramicidin combination and remained so during the short course of treatment.

Since a special watch was kept for any evidence of resistance or sensitization, an additional case treated with 'graneodin' ointment may be worthy of brief mention.

The patient, a child, was suffering from a severe, mixed infection and since the neomycin-gramicidin preparation has a wide range of antibacterial activity, it appeared to be the agent of choice. Response was relatively slow, but there was considered to be no justification for substituting one of the tetracycline drugs or any other antibiotic because alternative agents have a less effective antibacterial range, probably a higher sensitizing potential and often important systemic uses. The infection took five weeks to clear, but there was no evidence of bacterial resistance or allergic sensitization.

DISCUSSION

Leslie and Harvey (1954) reported that there was no evidence of the development of resistance or sensitization during the use of 'graneodin' ointment in 105 cases of various local infections, although in some instances, treatment was continued for four weeks. Waisbren (1956) stated that he encountered no cases of local sensitization after the use of topical neomycin. The 57 cases of impetigo in my series needed only short courses of therapy and in only the one special case mentioned was it necessary to continue treatment for as long as five weeks. The further findings, however, lend support to those already reported (Leslie and Harvey, 1954; McMaster, 1955) and it would seem that 'graneodin' ointment virtually fulfils all the desiderata for a local antibacterial preparation as regards efficacy, minimal risk of resistance and sensitization and avoidance of the local use of antibiotics which are given systemically.

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THE MISSING INFANT

By A GENERAL PRACTITIONER

Every general practitioner, as well as every consultant, must have his 'most interesting case'. The series of articles which are appearing in *The Practitioner* under the title of 'My Most Interesting Case' has prompted me to put on record the essential details of what I have regarded for many years as my own most interesting case.

THE FACTS

A young unmarried farmer asked me to call at his house. On arrival I found a young woman in bed who informed me that she had had a baby three days previously but could not get rid of the afterbirth. With no difficulty I expressed it and put it in the fire. The placenta was offensive and showed early signs of maceration. The patient's temperature and pulse were normal and continued so.

I inquired about the baby, but the patient obviously did not want to answer. She became rather evasive and muttered vaguely that it had fallen into the privy. I felt it my duty to search in the privy. This I did but failed to discover the body, although there were a few blood stains on the seat. In the farmyard I heard several pigs making a lot of noise as hungry pigs do. I wondered if the body could have been thrown to the pigs and I felt very strongly that it had.

I decided, however, to do nothing more and to go home, arguing that it had nothing to do with me and that in any case, on grounds of professional secrecy, I must not do anything. On second thoughts I began to wonder how I would stand if the matter came into the hands of the police as it most probably would through the talk of the neighbours, ever alert to a woman pregnant. I therefore consulted my solicitor who told me it was my duty, professional secrecy or not, to report the matter to the police.

THE POLICE

This I duly did. They never said anything to me but took the matter up and for several days could be seen searching the farm buildings and neighbouring fields. Nothing came of the search, but by this time I felt certain that the body must have been thrown to the pigs. No case was ever brought by the police. I was informed that without producing the body, or part of it, they could not bring a case of infanticide but it has always puzzled me why they did not bring a case of concealment of birth.

THE SEQUEL

Many years later the farmer, when well on in his cups at the 'local', boasted that he had thrown the body to the pigs. Indeed a gruesome but true story.

CURRENT THERAPEUTICS

CII.—CYCLOSERINE

By SOL KATZ, M.D.

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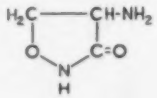
THE modern attack against tuberculosis includes the intelligent application of effective chemotherapy both as a definitive measure and in conjunction with the use of surgical methods, particularly those designed to remove residual cavitary and necrotic lesions.

Although numerous antituberculous agents have been introduced, streptomycin, *para*-aminosalicylic acid (PAS) and isoniazid remain the 'big three' which have weathered the storms of initial enthusiasm as well as prolonged clinical trial.

SOURCE

Cycloserine is the generic name of the newest antibiotic which entered the antimycobacterial field with a blare of optimism, only to find itself floundering as clinical trials were extended. It was first produced from an actinomycete, *Streptomyces orchidaceus*, and given the trade name 'seromycin'. Subsequent work (Harris *et al.*, 1955) indicated that another actinomycete, *Streptomyces garyphalus*, produced an antibiotic called 'oxamycin' which is chemically identical. Shull and Sardinas (1955) reported the isolation of an antibiotic (PA-94) which is identical and which is produced by *Streptomyces lavendulæ*. Cycloserine ('seromycin', 'oxamycin', PA-94) has the chemical structure of D-4-amino-3-isoxazolidone (Shull and Sardinas, 1955; Harned *et al.*, 1955):—



PHARMACOLOGICAL DATA

Cycloserine is water soluble and has a low molecular weight (102). It is palatable and readily absorbed from the gastro-intestinal tact. It readily diffuses into the pleural and the cerebrospinal fluid.

There is a wide variation in the blood levels obtained in different individuals receiving the same dose although fairly consistent levels are obtained repeatedly in the same person. This variability in blood levels may indicate individual difference in the metabolic handling of cycloserine. Differences

in the height of the blood levels obtained by various observers may also reflect differences in the colorimetric method used.

Welch *et al.* (1955) reported that the levels were higher than those obtained with most other antibiotics and that as the single dose was raised from 250 mg. to 1000 mg. the serum concentration at four hours increased from 2.25 mcg./ml. to 14.9 mcg./ml. The drug was still present in the serum at the end of twenty-four hours. When 0.5 g. was administered every six hours the concentration gradually rose to a peak of 43.2 mcg./ml. at the sixtieth hour.

In general, following the use of 0.5 g. of cycloserine twice a day, there appears to be an increasing level for the first two or three days of therapy. There is then a levelling off at a range between 20 and 40 mcg./ml. Moyer and Schwartz (1956) reported that 0.25 g. of cycloserine administered twice a day results in blood levels between 10 and 30 mcg./ml., with the majority between 20 and 30 mcg./ml.

High urinary concentrations of cycloserine occur with peak levels obtained eight hours after a single dose but with considerable amounts still present at forty-eight hours (Welch *et al.*, 1955). The concentration of cycloserine in the urine after repeated doses shows a pattern not unlike the serum concentration, in that the level increases and reaches a peak between the second and third day. Thus, when given in divided doses at six-hourly intervals, urine levels of 200 to 500 mcg./ml. are attained from daily doses of 0.5 to 1.0 g. (Herrold *et al.*, 1955).

EXPERIMENTAL STUDIES

In vitro studies.—In vitro antibacterial studies (Welch *et al.*, 1955) indicate that this antibiotic has relatively low activity against many gram-negative and gram-positive bacteria when compared with penicillin, streptomycin and the tetracyclines. These studies showed that cycloserine has broad-spectrum activity at fairly high concentrations, with no marked selectivity in favour of gram-negative or gram-positive bacteria. These investigators felt that it differed in its mode of action from other antibiotics and suggested that the drug exercises its antibacterial action by interfering with some component of an enzyme system or essential metabolite common to all of the bacteria tested. Cuckler and his associates (1955) showed that although cycloserine is a broad-spectrum antibiotic it appeared to be more effective against gram-positive than gram-negative bacteria. Harris and his co-workers (1955) demonstrated that cycloserine has a synergistic bactericidal action *in vitro* when combined with penicillin, bacitracin, oxytetracycline, chlortetracycline or chloramphenicol.

There has been some difference of opinion regarding the effect of cycloserine on *M. tuberculosis in vitro*. Some of these discrepancies may be based upon differences in technique employed as well as the variations in the strains of organisms being tested. Carefully executed studies by Cummings, Patnode and Hudgins (1955) indicate that cycloserine inhibits the growth of tubercle bacilli in concentrations of 10 mcg./ml. This is a level of sensi-

tivity at which tubercle bacilli are considered to be streptomycin sensitive. Furthermore, these authors showed cycloserine to be equally effective against a streptomycin-resistant strain and an isoniazid-resistant strain of *M. tuberculosis*. This corresponds to the results obtained by Cuckler *et al.* (1955) who showed that human, bovine and avian strains of tubercle bacilli, including those sensitive or resistant to streptomycin, viomycin, isoniazid, pyrazinamide and PAS, were inhibited by cycloserine in concentrations of 5 to 10 mcg./ml. There is suggestive evidence that cycloserine and isoniazid may behave synergistically *in vitro*. Similar synergism was not demonstrated for cycloserine and streptomycin.

In vivo studies.—Results in experimental non-tuberculous infections indicate that in contrast to its comparatively weak *in vitro* effects, cycloserine possesses a fairly high degree of *in vivo* efficacy. Furthermore, when cycloserine is combined with penicillin, streptomycin or oxytetracycline a synergistic action is noted in certain experimental infections (Cuckler *et al.*, 1955).

Cycloserine has proven relatively inactive in the treatment of experimental tuberculosis in mice (Welch *et al.*, 1955; Cuckler *et al.*, 1955) and guinea-pigs (Patnode *et al.*, 1955a). At higher dosage levels, Patnode and his colleagues noted a very slight therapeutic effect in guinea-pig tuberculosis. Furthermore, these same workers (Patnode *et al.*, 1955b) remarked that, although there was no marked difference between the treated guinea-pigs and the control animals, histopathological studies of the tissues from the treated group showed some evidence of healing. They speculated that if treatment had been continued, more significant healing might have been noted.

In contrast, Steenken (1955) reported that cycloserine exerted a significant therapeutic effect in bovine tuberculosis in rabbits with the results not as effective as streptomycin, isoniazid or viomycin but more so than PAS or amithiazone. Schmidt (1955) also observed distinct antimycobacterial activity of cycloserine in monkeys infected with human tubercle bacilli. More striking, however, were the good results he (Schmidt, 1956) obtained when the tuberculous monkeys were treated with cycloserine combined with isoniazid. This combination proved significantly more valuable than either cycloserine or isoniazid. In addition, cycloserine combined with isoniazid did not result in evident toxicity. In contrast, cycloserine combined with streptomycin proved considerably inferior to the cycloserine-isoniazid combination. These results differed from those of Cuckler and his associates (1955) who observed that the therapeutic effect from the concurrent use of cycloserine and dihydrostreptomycin in tuberculous mice was considerably greater than that produced by dihydrostreptomycin alone.

TOXICITY

Acute and chronic toxicity studies in animals indicate that cycloserine possesses an extremely low order of toxicity. In very large doses hyper-

activity, random movements, convulsions, lethargy and coma have been noted. In bold contrast stands its toxic effect in humans.

An extremely well-controlled double-blind study of toxicity was undertaken by the United States Public Health Service and reported by Murray (1956). Patients were excluded who had a history of mental illness, convulsions or head injuries. The toxic reactions recorded were convulsions, mental disorders, somnolence, dizziness, fever and chills. Of the patients receiving 0.5 g. of cycloserine twice a day, 11 (44 per cent.) experienced toxic reactions. In four of the 11 (16 per cent.) there were convulsions and in an additional four, mental or motor disorders. Seven (8 per cent.) of the patients who received an average of 0.5 g. of cycloserine daily had toxic reactions. Convulsions were the toxic effect in four of the seven. It is important to note that the frequency of convulsions in this latter group varied according to the frequency of drug administration. Thus, convulsions were noted in three (8 per cent.) of the patients who received 1 g. every second day, one (3 per cent.) of the patients who received 0.5 g. once a day and none of those who received 0.25 g. twice a day. This would suggest that the smaller the individual dose the less likely are toxic reactions. When a placebo was given for at least seven days to the eight patients who had had convulsions, there were no further symptoms. When cycloserine was started again, however, in four of these patients at one-half the original dose, one had another convulsion, one noted severe dizziness and diplopia and two had mild dizziness requiring a further reduction in drug.

In the Veterans Administration study on cycloserine reported by McLean (1956), convulsions occurred in 20 (8.7 per cent.) of the 229 patients receiving 0.5 g. of cycloserine twice a day. Approximately 20 per cent. of our patients receiving 0.5 g. of cycloserine twice a day have experienced *grand-mal* convulsions or severe twitching. All of these patients were very ill with far advanced tuberculosis and many were severe chronic alcoholics. On the other hand, Epstein and his associates (1955), who have treated the largest individual series of patients with cycloserine, were impressed with the extremely low incidence of toxicity. Most of their patients received 0.25 g. four times a day. This difference in dosage may have a bearing on toxicity.

We were unable to correlate strictly the height of the cycloserine blood level and its relationship to convulsions. McLean (1956) also observed blood levels of low magnitude (less than 30 mcg./ml.) in some of the patients with convulsions. On the basis of current experience, however, it would appear that a low incidence of neurotoxicity can be expected on a dose schedule of 0.25 g. twice a day.

In our experience the significant toxic reactions to cycloserine occur within a few days to four weeks after the onset of therapy, with most of them being observed in the first two weeks. Murray (1956) also noted toxicity within the first 16 days. Dosage seems to influence the frequency

but not the time of onset of toxicity. Electroencephalograms were of no help in the evaluation or anticipation of toxicity, for abnormalities were seen in our patients before treatment and during treatment in the group with and without toxic manifestation. Murray (1956), in the U.S. Public Health Service Study, was also unimpressed by the electroencephalographic findings, for changes were recorded with equal frequency among toxic and non-toxic patients receiving cycloserine and a placebo.

CLINICAL STUDIES

For the most part clinical studies have been confined to the use of cycloserine in urinary-tract infections and tuberculosis. There is one report (Lillick *et al.*, 1956) on the use of cycloserine in a wide variety of non-tuberculous conditions including respiratory infections, otitis media, diarrhœa, local skin abscesses and herpetiform lesions. Excellent results were seen in 9 per cent., good results in 70 per cent. and poor results in 21 per cent. The clinical results were stated to be comparable to those expected from a broad-spectrum antibiotic in infections due to susceptible organisms.

URINARY INFECTIONS

Ideally, in the treatment of renal infections the antibacterial agent employed should achieve adequate concentrations in the renal tissues as well as in the urine. On the other hand, in the management of infections of the excretory urinary tract it is quite possible that high urine levels of the chemotherapeutic agent may be all that is required. Since concentration in the tissues is related to blood concentration, most effective antimicrobial agents used in the therapy of renal infections achieve a blood level that is bacteriostatic when applied *in vitro* against the causative organism. Cycloserine presents an exception to this concept for, although it produces relatively high blood concentrations, they are not sufficiently high to explain the good therapeutic results obtained in renal infections due to organisms with *in vitro* resistance much higher than the levels reached in the blood (Welch *et al.*, 1955). This has prompted speculation regarding the mode of action of cycloserine. Welch and his associates suggest that the drug may alter physiological conditions in the host in such a way as to produce unfavourable environment for the growth of bacteria. They also propose that cycloserine may interfere with an enzyme or may block metabolic pathways necessary for multiplication or survival of micro-organisms. Sufficiently high urine levels of cycloserine are obtained to explain the effectiveness of this antibiotic in infections of the excretory urinary tract due to even the more resistant organisms.

Herrold and his associates (1955) reported 60 per cent. success from the use of cycloserine in the management of stubborn upper and lower urinary-tract infections. The predominant organisms were various species and mixtures of gram-negative and gram-positive organisms. Welch and his col-

leagues (1955) also present data submitted by Dr. G. R. Nagamatsu which indicate the clinical efficacy of cycloserine in the treatment of resistant infections of the genito-urinary tract.

TUBERCULOSIS

Tremendous differences of opinion exist regarding the value of cycloserine in the management of human tuberculosis. Epstein *et al.* (1955), in the first clinical report on cycloserine in human tuberculosis, expressed extreme enthusiasm for this mode of therapy in patients with acute tuberculosis previously untreated, as well as in those with chronic far advanced tuberculosis who had failed to respond to various combinations of streptomycin, isoniazid and PAS. All eight patients with acute tuberculosis who had not received previous therapy showed striking clinical improvement as well as a response judged by radiological changes. In addition, there was conversion of sputum from positive to negative in all cases. In the 29 patients with chronic, far advanced tuberculosis who had failed to respond to other forms of treatment, there was clinical improvement in 28 and rœntgenographic improvement in 20. Sputum conversion occurred in 76 per cent.

This is indeed a remarkable achievement. This type of tuberculosis, chronic and resistant to conventional therapy, is the hard-core problem in the management of tuberculosis today. To add to this happy therapeutic picture, these authors were impressed with the low toxicity of cycloserine. In a report on an extended series of cases, Epstein and his colleagues (1956) continue to be pleased with the results attained with cycloserine alone, both in acute previously untreated disease as well as in chronic resistant tuberculosis. Furthermore, although their data were incomplete, they did not observe the development of resistant tubercle bacilli. In addition, these investigators noted that combination therapy, employing either isoniazid or streptomycin along with cycloserine, offered added advantages and permitted a reduction in dosage of cycloserine to 0.5 g. a day without any loss in efficacy and with a further reduction in an already low toxicity.

The Veterans Administration began a carefully planned study of cycloserine in March 1955. One hundred and ninety-four previously untreated patients were chosen by random allocation for treatment with cycloserine alone, 0.5 g. twice a day (93 patients), and isoniazid plus PAS (101 patients). An additional 138 patients who had been previously treated unsuccessfully with other drug regimens also received cycloserine alone, 0.5 g. twice a day. At the 15th Conference on the Chemotherapy of Tuberculosis sponsored by the Veterans Administration, Army and Navy, and held on February 6-9, 1956, the reports (Maclean, 1956; Livings, 1956) indicated the following:—

In the original treatment group significant radiological improvement following six months of treatment occurred in 84 per cent. of the patients receiving isoniazid and PAS, compared with 63 per cent. of those receiving cycloserine alone. Sputum conversion at six months occurred in 96 per cent. of these receiving isoniazid and PAS, compared with 63 per cent. of those who received cycloserine. Cavity closure

also was observed more frequently in the patients given isoniazid and PAS. Clinical relapse or radiological worsening was noted three times more often in the cycloserine group. Added to this obvious inferiority of cycloserine was the striking incidence of neurotoxicity.

In the retreatment patients who were given cycloserine there was only 10 per cent. radiological improvement and 11 per cent. sputum conversion at six months.

In addition, bacterial resistance occurred rapidly in both original and retreatment groups of patients and correlated with treatment failure or relapse. Cummings (1956) reported that resistance to cycloserine should be defined as growth in culture tubes containing 20 mcg./ml. of cycloserine equal to growth obtained in drug-free media. He stated that if the 10 mcg./ml. level were selected, approximately 15 per cent. of tubercle bacilli would be resistant to cycloserine before treatment was instituted.

Because of the obvious shortcomings of cycloserine alone, the Veterans Administration is no longer pursuing the investigation of this drug as a single agent in the management of tuberculosis.

In the U.S. Public Health Study reported by Murray (1956) radiological changes at 12 weeks indicated that only 34 per cent. showed some improvement on 1 g. of cycloserine daily and 20 per cent. on 1 g. every second day. On the other hand, about 10 per cent. of patients on a placebo, or receiving 0.5 g. of cycloserine daily in one or two doses, showed slight improvement radiologically. Thus, the relatively non-toxic regimens of cycloserine resulted in no more radiological improvement than a placebo. Furthermore, worsening, as assessed by x-rays, occurred in 15 per cent. of those receiving 0.5 g. of cycloserine a day in a single dose and in 25 per cent. of those receiving 0.25 g. twice a day. The inevitable conclusion from this study was that in the mean of previous treatment failures, cycloserine, in doses with some therapeutic efficacy, is highly toxic whilst non-toxic doses are therapeutically ineffective.

Our experience with the use of cycloserine was disappointing in the treatment of acute pneumonic tuberculosis in patients with marked toxicity. Subjective response was infrequent or delayed and objective evidence of efficacy including x-ray improvement was rare. Also, sputum conversion was unimpressive.

It would appear that as a single drug cycloserine is disappointing in the management of tuberculosis, whilst the toxicity at a dose level of 0.5 g. twice daily is prohibitive. The experiments using cycloserine and isoniazid in monkeys are quite provocative. It may be therefore that smaller daily doses of cycloserine when combined with isoniazid will be non-toxic yet effective in the therapy of human tuberculosis.

SUMMARY AND CONCLUSIONS

Cycloserine ('seromycin', 'oxamycin', PA-94) is an antibiotic of low molecular weight which is readily absorbed from the gastro-intestinal tract and easily diffuses into body fluids. Although it possesses low *in vitro* activity of the broad-spectrum type, it usually inhibits tubercle bacilli in concentrations of 20 mcg./ml. or lower.

Discrepancies in *in vivo* activity exist but, in general, cycloserine demonstrates better *in vivo* efficacy in certain experimental infections than its *in vitro* effect against the same organisms. Experimental tuberculosis in mice and guinea-pigs is not favourably influenced by cycloserine, whilst tuberculosis in rabbits and monkeys is benefited.

Toxicity for animals is low but neurotoxicity in man, especially twitchings and convulsions, occurs sufficiently often at a dose of 1.0 g. a day to limit the usefulness of cycloserine.

Clinical studies indicate that cycloserine is valuable in the management of urinary-tract infections. There are differences of opinion, however, regarding its value in the management of human tuberculosis. Certainly, cycloserine is far inferior to the use of isoniazid in combination with PAS. In addition, the apparent rapid development of bacterial resistance further limits its usefulness. It is possible that smaller and therefore non-toxic doses of cycloserine combined with isoniazid may show promise in the therapy of tuberculosis.

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MY MOST INTERESTING CASE

XVII.—A GRANULOMA OF UNKNOWN ORIGIN

By H. MORRISTON DAVIES, M.D., M.Ch., F.R.C.S.

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The patient was a woman of 42 from the Isle of Man. In April 1948, x-ray films of her chest were submitted to me by Dr. Armour. She had had a cold in October 1947 and afterwards complained of lassitude. In February 1948, she became acutely ill, and was given penicillin and sulphonamides, and the pyrexia settled. An x-ray, however, revealed partial collapse of the right lower lobe. She was therefore admitted to the Chest Unit at Broadgreen Hospital, Liverpool, for bronchoscopy.

CLINICAL FINDINGS AND COURSE

On admission, she was found to have a slight cough, but no sputum or hæmoptysis. She complained of lassitude and gave a history of loss of weight of over 14 lb. (6.5 kg.) in the previous eighteen months. The physical signs were those of collapse only. The white blood count was 2,800 per c.mm., with 18 per cent. of lymphocytes. On bronchoscopy the only abnormality found was rugination of the right lower lobe bronchus, some narrowing of the dorsal division and some rigidity. No growth was seen. A biopsy of the mucosa in the affected region showed diffuse lymphocytic infiltration.

The case was discussed at the Liverpool Chest Unit clinic and the probable diagnosis of a bronchial carcinoma was agreed. On June 6, 1948, Mr. Temple did a right pneumonectomy. On opening the chest he found the lower lobe to be invaded by a mass of growth, which was adherent to the diaphragm and to the wall of the left auricle, a part of which was resected with the inferior pulmonary vein. The resected specimen was reported on by Dr. Whitwell as follows:—

> 'Appearances suggest carcinoma but section shows that histologically it is a rather hyperplastic tuberculous granulation tissue, and there is no tumour present. The lower lobe bronchus shows scattered foci of tuberculosis, and, more peripherally, the apparently firm areas are composed of dense caseous matter'.

In view of these findings the patient was put on a course of streptomycin (then a gramme a day for six weeks). On July 19, 1948, a polythene pack was put into the right side of the chest to prevent mediastinal displacement to the right and hyperexpansion of the left lung. A month later she returned home. Her general condition was fairly good but she had not regained her former weight.

Reports sent from the Isle of Man some six to nine months later showed a rapid deterioration. Early in July 1949, 'she was very weak with large

masses of neck glands, some hard but not stony hard; some relatively free and elastic, but none showing any signs of caseous breakdown'. Mr. Temple asked for a biopsy of a gland and one was removed from the neck. The pathologist's report stated:—

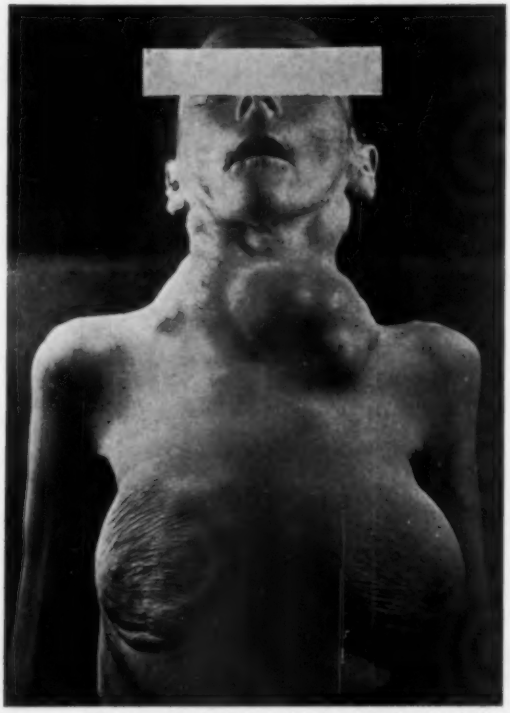

FIG. 1.—The terminal phase, showing gross emaciation and massive collar of enlarged glands in the neck.

'This has a small necrotic centre where there is some remains of the original tissue; the surrounding gland tissue is fibrosed and shows a proliferation of endothelial cells. There is intense eosinophil proliferation and only one or two small giant cells. The appearance suggests a non-specific type of granuloma with some similarity to Hodgkin's disease'.

Towards the end of August the patient was still severely ill and Mr. Temple flew over to see her. He reported that clinically she was an obvious example of Hodgkin's disease. She was emaciated; there was a huge collar of glands (fig. 1) and the spleen was enlarged. There were no abnormal physical signs in the remaining lung. She died a few days later.

POST-MORTEM FINDINGS

The post-mortem report by Dr. Pantin was:—

'The body was very emaciated with a bulky collar of glands stretching from one posterior triangle to the other, extending in a continuous chain with others at the apices of the pleura; on the left was a lobulated mass adherent to the lung. Enlarged glands were also noted forming an aortic chain from the thorax to beyond the bifurcation of the aorta. The spleen was four or five times the normal size and had the "hard-baked" appearance of Hodgkin's disease (fig. 2). The liver was normal in size and contained some small white nodules. The mesentery and intestines were free from nodules'.

Some of the material was sent to Dr. Whitwell who noted:—

'The majority of the lymph glands are large and consist of a mass of necrotic

tissue with a thin peripheral rim of non-necrotic tissue. The microscopic appearance suggests the diagnosis of atypical Hodgkin's disease. The necrotic tissue is quite firm and has not lost all structural detail as with caseation; the cells in the surviving tissue are very pleomorphic and contain some mirror-image giant cells, endothelial cells, lymphocytes and fibroblasts, with occasional eosinophils'.

He then re-examined the original sections of the lung and found that the areas of necrosis exceeded those of caseation. He continued:—

'There is a profuse giant-cell and epithelial reaction around the necrotic foci, and many foreign body type giant cells contain inclusions such as are seen in sarcoidosis and sometimes in tuberculosis (fig. 3). There are no mirror-image giant cells, eosinophils, or any of the pleomorphism of the later material [that obtained at necropsy]. The microscopic appearance of the lung suggests an atypical tuberculosis'.

FIG. 2.—Photograph of spleen removed at necropsy, showing gross enlargement and 'hard-baked' appearance of Hodgkin's disease.

He summed up as follows:—

'The association of atypical tuberculosis with atypical Hodgkin's disease a year later, and the further different appearance of a non-specific granuloma in the biopsy during the year suggests that this is a specific disease of granulomatous type of unknown origin'.

DISCUSSION

There can be no doubt that this patient suffered from a single disease entity. Clinically it presented as a primary neoplastic disease of the lung and, unless a satisfactory biopsy could have been obtained, the line of treatment followed was inevitable. The subsequent histological finding was very suggestive of tuberculosis and treatment from then on was modified appropriately. Thereafter the disease behaved like any other case of rapidly progressive generalized reticulo-sarcoma.

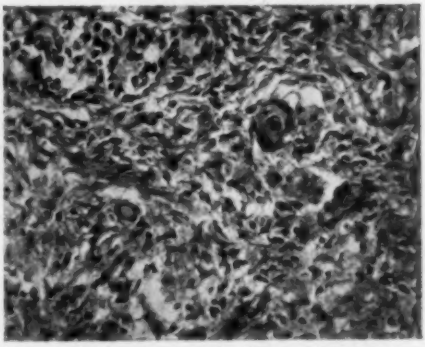

FIG. 3.—Microphotograph of lung, showing giant cell containing inclusion and epithelial reaction (lower left). (x 366)

The histology of the original lung lesion suggested atypical tuberculous disease; that of the terminal condition atypical Hodgkin's disease, whilst

the gland biopsy showed an intermediate type of pathology linking the other two. Hodgkin's disease first manifesting itself as a tumour of the lung is not unknown. Two subsequent patients in the same unit have had lung resections for 'tumours' that revealed a histological picture very similar to this case. One has since died of generalized tuberculosis and the other has been proved to be suffering from tertiary syphilis.

Hodgkin's disease, moreover, is the name given to a pathological response and not to an etiological entity. Other pathological responses may be identical, even when due to different etiological agents: for example, erythema nodosum due to infection with tuberculosis or coccidioidomycosis. It is therefore not unreasonable to suggest that the condition we know as Hodgkin's disease may be due to any of several etiological factors. In this case the first response resembled that produced by the tubercle bacillus, but became gradually modified to the typical picture of reticulosis. It is perhaps from these borderline cases that clues may be found that will ultimately reveal the etiology of the granulomas.

REVISION CORNER

EOSINOPHILIA

In common parlance the term eosinophilia is usually interpreted as meaning an increase of the circulating eosinophilic granulocytes in the blood above their normal range. More properly it should be used when considering both blood and tissue increases of such cells, changes which by no means necessarily run in parallel.

To most practitioners mention of eosinophilia in relation to a case immediately brings to mind diagnostic possibilities of asthma, a skin disorder or helminth infestation, but there is a wide range of disorders associated with eosinophilia—an allergic response to some exogenous or endogenous protein antigen probably being the common denominator of them all. Many studies have been attempted to unravel the mysteries of the eosinophilic leucocyte and, whilst recorded observations abound, a clear understanding of the general phenomenon of eosinophilia is still lacking.

BLOOD EOSINOPHILIA

The normal numerical range of circulating eosinophils is dependent upon physiological variables, the method of enumeration employed and the skill and patience of the individual counting the cells. Whilst a moderate or marked degree of eosinophilia can easily be recognized during a short scrutiny of a well-stained blood film, lesser degrees of the change are more difficult to assess and there is general agreement that 'chamber', or so-called 'wet', counts are much more reliable and reproducible than those values

obtained by differentiating, say, 200 leucocytes in a blood film. The diluting fluid described by Randolph, or one of its modifications, can be recommended as the best way of assessing the number of eosinophils in blood. The diluent used in my laboratory is made up as follows:—

0.1 g. of phloxine is dissolved in 50 ml. of distilled water and then 50 ml. of propylene glycol and 0.4 ml. of 20 per cent. sodium carbonate are added. This solution, which keeps well, is filtered immediately before use.

Using a 1 in 10 or 1 in 20 dilution of blood in a leucocyte pipette, triplicate counts are made using Fuchs-Rosenthal counting chambers. Ordinary Neubauer hæmocytometer chambers can also be used—an area of at least 36 square millimetres being covered in the course of a count. Under the high power of the microscope the eosinophils stand out sharply and are easily recognized.

Using such a technique the eosinophil count of an apparently normal individual may be up to 400 per c.mm.; values of 150 or thereby per c.mm. are those most often encountered. In asthmatic subjects eosinophil counts of up to 2000 per c.mm. are quite often found, whilst in trichiniasis, angioneurotic œdema and tropical eosinophilia values may on occasion reach 15,000 per c.mm. or more.

ORIGIN, FUNCTION AND FATE OF EOSINOPHILS

Whilst there have been differences of opinion over the origin and nature of the granules of the eosinophil, most authorities would consider that these cells are produced in the bone marrow, eosinophilic myelocytes and metamyelocytes being found in normal marrow smears in small numbers. The mature cell, which rarely has more than two nuclear lobes, is motile and shows phagocytic activity which is less than that of the neutrophil. It is thought that the granules are composed of a phospholipid, a protein and desoxyribonucleic acid. The hypothesis that their function is to carry histamine and histamine-like substances and so, presumably, 'detoxicate' the body of products of major and minor allergic responses is an attractive one and prompts the question as to where the circulating eosinophils go and what is their fate?

The careful studies of Vaughn (1953) in experimentally induced eosinophilia give evidence that blood eosinophils travel to the submucosa of the bronchial tree, nasopharyngeal area and intestinal tract, from where they may be excreted or else taken up by lymphatics and ultimately destroyed in the spleen. This view is supported by evidence showing that following blood eosinophilia bronchial secretions contain many eosinophils at a time when they have subsided in numbers in the blood stream. The hypothesis that Charcot-Leyden crystals are derived from eosinophils also has significance in this respect. Moreover, the eosinophilia often observed after splenectomy could be interpreted as being the result of loss of a disposal centre for eosinophilic cells.

The concept that accumulation of eosinophils around bronchioles and blood vessels in the lungs prior to their excretion or disposal should be remembered in connexion with the unusual radiological appearances seen

in those allergic disorders known as Loeffler's syndrome or tropical eosinophilia. Whilst, in the tropical group, local reaction due to migration of worms may contribute to the lung changes, such tissue infiltration by eosinophils from the blood stream is an important factor.

EOSINOPHILS AND ADRENOCORTICAL EFFICIENCY

The introduction of corticotrophin gave a new importance to eosinophils. The phenomenon that in health the number of blood eosinophils falls within a few hours of an injection of corticotrophin forms the basis of what is now known as the Thorn test. When adrenocortical function is absent or impaired, as in Addison's disease, no such eosinopenic effect of corticotrophin is observed. Although with proper technique this test can be a useful rough guide, it should not be used as the sole evidence of adrenocortical disorder (see *The Practitioner*, 1955, **175**, 583). The 'alarm reaction' occurring with injuries, burns, shock and acute infections is associated with a fall in blood eosinophils, and the recent studies of Sevitt (1955) have shown that those dying about forty-eight hours after injury show a marked reduction in eosinophils in the spleen and such a necropsy finding can be regarded as indicative of adrenocortical hyperactivity. Why the fall in numbers of eosinophils occurs has not yet been fully explained but it is likely that rapid mobilization of circulating eosinophils to the tissues with subsequent sequestration is the mechanism concerned, rather than any effect on bone marrow production of the cells. An eosinopenic effect has also been observed after either oral or parenteral administration of adrenaline and this appears to be independent of adrenocortical function.

THE SIGNIFICANCE OF BLOOD EOSINOPHILIA

Whilst knowledge of certain mechanisms concerned with the number of circulating and tissue eosinophils has increased, the nature of the antigenic or sensitizing substance regarded as being concerned with the stimulus of eosinophilia remains obscure.

From the clinical standpoint the finding of blood eosinophilia can be regarded as objective evidence of 'sensitivity' in the widest sense and the allergic process concerned may range from that associated with mild hay fever or urticaria to that of a serious helminth infestation such as trichiniasis, or that of carcinoma or 'reticulosis'. Particular diseases which may be associated with blood eosinophilia are numerous but a broad classification (modified from Wintrobe, 1951) is as follows:—

(1) Skin conditions of allergic type, hay fever and angioneurotic œdema.

(2) Pulmonary disorders: Bronchial asthma
Loeffler's syndrome
Tropical eosinophilia
Infiltrative eosinophilia.

(3) Helminth infestations, particularly when worms are invading tissues. A patient with a walled-off hydatid cyst may show no change in eosinophils.

Absence of eosinophilia does not exclude the presence of worms.

(4) During convalescence following acute infections (e.g. glandular fever), and in those undergoing radiotherapy.

(5) Blood diseases: Chronic myeloid leukæmia (a very rare variety of this, eosinophilic leukæmia, is described)
Polycythæmia vera
Some of the 'reticulosis' group (it is by no means constant in classical Hodgkin's disease).

(6) Occasionally in carcinomatosis and so-called collagen diseases such as polyarteritis nodosa, and lupus erythematosus; it can be associated with toxoplasmosis and coccidioidomycosis.

(7) Drug reactions—e.g. following penicillin or liver extract injections—even although the patient shows no constitutional disturbance.

(8) Following splenectomy.

(9) Familial eosinophilia which is probably evidence of a familial allergic tendency.

On occasion blood eosinophilia can act as a signpost in making an important precise clinical diagnosis. Nevertheless, its lack of specificity and its inconsistency in many disorders with which it may be associated require emphasis. This does not take away from the potential usefulness of this time-honoured hæmatological finding, the interpretation of which the physician must make in the light of the clinical history and examination. Often the phenomenon of eosinophilia is accounted for easily—indeed its presence is expected. In some cases it may provide quite a new line of thought in an approach to a clinical problem, but there are others in which a persistently raised eosinophil count can be as inexplicable as the nature of the cells themselves.

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INSECT BITES AND STINGS

So far as Great Britain is concerned, insect bites and stings are seldom dangerous, but their nuisance value can be considerable, as many a Sassenach has learnt to his cost when attempting to holiday in a midge-ridden district of Scotland. In this short note I propose to deal only with black-flies, midges, mosquitoes, horse-flies, ants, bees, wasps, and hornets.

BLACK-FLIES ('SAND-FLIES')

Simuliidæ are of worldwide distribution. The early stages of all of them are passed in running water—the larvæ being found attached to rocks.

They have a great range of flight and in Britain have been found over two miles from their nearest breeding place. All species are blood-sucking insects. The Golubatz fly which breeds in the river Danube occasionally causes enormous losses among domestic animals, and a census in 1923 revealed the loss there of almost 20,000 domestic animals, as well as many wild animals, all in the latter half of April. Death in animals is due partly to loss of blood and partly to the poisonous effects of the bites. Certain parts of Northern Canada are uninhabitable during the summer because black-flies are so numerous. A species of black-fly is responsible for the transmission of the nematode causing human onchocerciasis in West Africa.

Many species of Simuliidæ are found in Britain and almost without exception the breeding grounds are small streams with gravelly bottoms which dry up in the summer time. The bite may be more painful than a mosquito bite and causes a hard swelling which may persist for weeks. From the point of view of human medicine they have only a nuisance value, but to agriculturists they are important owing to the annoyance they cause to domestic animals including horses and cattle.

BITING MIDGES

These tiny flies comprise the family of Ceratopogonidæ, are biologically related to Simuliidæ and have well-developed biting mouthparts. There are nearly 150 species in Britain but only a minority of them are blood-feeders. The majority feed on other small insects or on plant juices. The genus, Culicoides, is the only blood-feeding genus which occurs in Britain. In West Africa culicoides is the host of the worm, *Filaria perstans*, but in this country midges are not carriers of human disease though they do have an enormous nuisance value. They are major pests in Scotland where they constitute a serious handicap to the tourist industry of the Trossachs and elsewhere in the July-September period. Agriculture is also handicapped. *Culicoides impunctatus* is the midge incriminated and efforts are being made to eradicate breeding places.

As with other insects, the effect of the bite varies with different victims as well as with different species of midge. In those sensitized, irritation starts immediately and is followed in six to twelve hours by a large œdematous swelling, often with a blister on top. Irritation is intense. The bitten face or limb is often stiff and very painful, and there may be regional adenitis. This particular reaction is not due to secondary bacterial infection and antibiotics have no place in treatment.

MOSQUITOES (GNATS)

Twenty-six different kinds of mosquito occur in the British Isles, and include some varieties of the malaria-carrying genus, Anopheles. *Ædes ægypti* is the vector for the virus of both dengue fever and yellow fever and *Culex fatigans* is the vector for filariasis. In this country, thanks to efficient public health control, these diseases are not seen but mosquitoes, chiefly varieties of the genus, Culex, have a great nuisance value.

The reaction from the bites of mosquitoes, which are allergic and based on specific sensitization, can be extremely severe and large bullæ are often produced. There is an immediate reaction which is urticarial, slightly itchy and disappears within an hour, and a delayed reaction which is very itchy, develops after 24 hours and lasts for several days. The drainage of swamps and removal of breeding places, and the use of DDT sprays to kill the adult mosquitoes help to make parts of our own countryside more comfortable in the summer months.

HORSE-FLIES (CLEGS)

These vicious insects belong to the family of Tabanidæ, and because of their large size (up to one inch in length) are formidable opponents. They are of worldwide distribution and about 28 species are found in the British Isles. They are found particularly in fields and woods and are most troublesome in good weather conditions: indeed they do not like dull weather or shade. The female alone drinks blood; the male may be seen on flowers or on the surface of pools or streams. Any animal species, including man, may be attacked and in the British Isles they are important pests of cattle and horses. In certain parts of Russia, Tabanidæ are so numerous and vicious that animals cannot be taken out during the daytime and farming is actually carried on at night.

The most remarkable thing about clegs is the length of the proboscis which allows the insect to bite through clothing. Their approach to the victim is usually not noticed, though some species make a humming sound, but the proboscis being large the 'bite' produces a sharp painful sensation. Again, since the bite is a large one there is often oozing of blood after the insect has fed and in animals this may amount, after repeated attacks, to serious blood loss. While in the act of feeding the insect can easily be killed. Tularæmia and the parasitic worm Loa-Loa are carried by Tabanidæ in other parts of the world, but disease is not transmitted by these insects in this country.

Some people may be extremely sensitive to cleg bites and often a large blister with considerable surrounding œdema and associated adenitis is produced. Because of the large size of the wound inflicted by the proboscis, sepsis is a common complication of cleg bites.

TREATMENT

For the immediate treatment of bites due to black-flies, midges, mosquitoes and horse-flies, frequent and liberal applications of cool calamine lotion are certainly soothing. Expensive hydrocortisone and antihistamine creams are probably not better than calamine, and antihistamine drugs given by mouth are of doubtful value in this type of reaction. Dimethyl phthalate is an effective repellant but, of course, all parts of the skin and clothing have to be treated.

ANTS, BEES, WASPS AND HORNETS

The bites of these insects differ from those of the others described since a toxic substance is actually injected into the skin and the bite itself is a form of defence against an opponent. These stings are therefore always painful and may be dangerous, especially if the sting is in the mouth or throat or should anaphylactic shock develop.

The stings from ants, bees and wasps are not treated similarly because bee venom contains formic acid whereas ant and wasp venoms are alkaline. In addition, unlike the ant and wasp, the bee leaves part of its sting in the wound and care must be taken or more venom will be squeezed from the sac on the sting into the wound. The appropriate antidote for a bee sting is ammonia, bicarbonate of soda or washing blue and it should be dabbed on and not rubbed in. On the other hand, the poison of the wasp contains large quantities of hyaluronidase, and 2 per cent. of histamine, and is neutral or alkaline. The appropriate antidote for ant, wasp and hornet stings is vinegar or lemon juice.

If the patient has been sensitized on a previous occasion and is anaphylactic there may be immediate and profound vasomotor collapse and death within minutes. In other cases there may be generalized urticaria and angioneurotic œdema, perhaps with nausea, vomiting and respiratory distress. Adrenaline (10 minims [0.6 ml.] of 1 : 1000 solution) should be given immediately if signs of shock are present. It is possible that cortisone and corticotrophin will have a part to play in the treatment of collapse of this type.

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NOTES AND QUERIES

Treatment for Tapeworms

QUERY.—Is there any new treatment for tapeworms? On several occasions recently, despite rigorous starvation, I have failed to get the head away with filix-mas treatment.

REPLY.—Yes, either mepacrine or 'dichlorophen' should be tried.

(1) *Mepacrine.*—After two days' starvation, 1 g. of mepacrine is given crushed and suspended in milk. Half an hour later a strong saline purge is given to remove the worm.

(2) '*Dichlorophen*' (May & Baker).—This substance usually kills the worm, which is thereafter digested, so the head cannot be found in the stools, and consequently the result of the treatment cannot be assessed except by waiting for three months, after which, if segments have not reappeared, a cure can be assumed. Preliminary starvation and subsequent purgation are unnecessary. The drug is given in the morning in a single dose of one tablet (0.5 g.) per 16 lb. (7.3 kg.) body weight. There are no side-effects other than slight colic and looseness of the bowels.

D. R. SEATON, M.B., M.R.C.P., D.T.M.

B.Z.55 in Diabetes Mellitus

QUERY.—My diabetic patients wish to know whether the new oral form of treatment for diabetes mellitus, which is receiving so much publicity at the moment, is really effective. As successful results are claimed, I would be grateful for an expert opinion.

REPLY.—B.Z.55, which is a sulphonamide pre-

paration, has been used for some time in Germany and is at present being given a clinical trial both in this country and in the United States. It is too early to express any definite opinion on the place, if any, that it may have in the treatment of diabetes mellitus, but it would appear reasonably certain that it is not to be regarded as a substitute for insulin and that the majority of diabetics who require significant doses of insulin to control their disease are not benefited by it. There does, however, appear to be a group of relatively mild cases, as yet not defined, in whom B.Z.55 produces a definite lowering of the blood sugar and a consequent reduction in glycosuria. There is no evidence that it produces any serious toxic effects on the liver or other organs, but mild side-effects such as skin rashes and giddiness have been reported.

The mode of action of this new drug is not yet known, but it has been suggested that it may produce its effect by inhibiting insulinase or possibly glucagon; experimental evidence is at present inconclusive. It appears to have no place in the treatment of the severe diabetic and has no significant action on ketosis.

It is to be hoped that the limited supplies of B.Z.55 at present available will be restricted to further research on its properties and the indications for its use in diabetes.

WILFRED OAKLEY, M.D., F.R.C.P.

Early Diagnosis of Simple Glaucoma

QUERY.—I have a patient, aged 42, who complains of seeing 'rainbow-halos' on any naked lights (electric), day or night. This has been going on for the past four weeks. The patient is very fit, has no headaches, no glycosuria, and general examination is negative. Ophthalmologists find his eyes perfectly normal. He does not wear glasses and his vision has not deteriorated over the last twelve months. Glaucoma, naturally, is being considered, but so far has been excluded. I would be grateful for suggestions in this case.

REPLY.—The dramatic onset of acute glaucoma is in bizarre contrast to the insidious way in which chronic simple glaucoma makes its appearance. In the latter form of the disease there is a period of time in which meagre subjective symptoms and an almost total absence of objective signs make diagnosis difficult. When cupping of the optic disc is found, the disease is already well-established. Transient halos, often blue in colour, are very suggestive of rises in intraocular tension in which the corneal epithelium becomes œdematous and dull; but some forms of chronic conjunctivitis cause a glairy film to form over the cornea and halos to be produced. If this is present it should be dealt with either by specific treatment or by using the following lotion, diluted half and half, twice a day:—

Chlorbutol	1 grain (0.06 g.)
Sodium chloride	12 grains (0.8 g.)
Cherry-laurel water	20 minims (1.2 ml.)
Elderflower water or distilled water to	1 fluid ounce (28.5 ml.)

If glaucoma is suspected and cannot be confirmed by a clinical examination provocative tests should be carried out, such as:—

(*a*) Dark-room test, in which after 40 minutes in a dark-room the tension, as estimated by the Schiotz tonometer, is raised.

(*b*) Reading test. The patient is made to read small print or do fine embroidery in artificial light for 30 minutes. Halos may appear and the tension may rise as much as 10 mm. Schiotz.

(*c*) Decubitus test, in which the head is lowered and the tension rises.

(*d*) Caffeine test, in which 30 minutes after drinking strong coffee the tension rises 20 mm.

Other provocative tests with miotics can be used. When using the tonometer the cornea is anæsthetized with 1% amethocaine. These tests, as well as the 24-hour test in which the tension is taken every 3 hours, day and night, are best carried out in hospital.

There is, however, a simple *therapeutic test* in which drops of pilocarpine, 1%, are instilled at 9 a.m. and 9 p.m. If this succeeds in eliminating the halos there would be strong grounds for supposing that glaucoma is responsible. The drops in a lesser concentration (0.25% or 0.5%) can then be continued therapeutically, with control intermissions during which halos may once more occur. Frequent observation is essential in suspected cases and a rapid increase in presbyopia is significant.

It must be emphasized that early simple glaucoma is one of the most difficult diseases in which a dogmatic diagnosis can be made.

A. MCKIE REID, *M.C.*, T.D., F.R.C.S.

Nocturnal Frequency of Micturition

QUERY.—I would be grateful for advice on a personal problem. I am 54 years of age and from childhood have suffered periodically from nocturnal frequency of urine when I cannot sleep or when I am in a state of tension. Trying to overcome the habit makes it worse. A urological examination reveals nothing abnormal. The amount of urine passed is very small and of a very low specific gravity. I have tried taking barbiturates but I only get a hangover next day and the frequency still persists.

I am aware that the condition is psychogenic, but I have no worries whatsoever. I might

mention that my father had, and both my children have, the same complaint. I would be grateful for advice regarding treatment.

REPLY.—This problem seems to me to be insoluble. Frequency of micturition during mental stress, or in a state of tension, is extremely common and usually occurs only in circumstances which do not repeat themselves often, such as taking examinations or running in races. If states of tension which produce these symptoms occur much more frequently than they should, owing to the mental constitution of the patient, the frequency of micturition is likely to be very troublesome.

One method of treatment which is sometimes successful in lowering the intensity of mental tension is to take a small dose of phenobarbitone (½ grain [30 mg.] three times a day) regularly. This cannot possibly cause a hangover, and it is better than taking sedatives as a specific remedy when the state of tension occurs.

PROFESSOR V. W. DIX, M.B., M.R.C.P., F.R.C.S.

Pregnancy During Lactation

QUERY.—I have a patient who is breast-feeding her three-month-old child. She menstruated six weeks after the birth of the child. She has had no further period and queries a further pregnancy. What are the chances of a pregnancy at this stage? Are the urine tests for pregnancy still applicable?

REPLY.—Pregnancy is not common within the first three months of lactation, but lactation is no complete barrier to conception. The earlier menstruation is resumed after a birth, the greater is the tendency to irregularity. Having begun as early as six weeks in this woman it could well be that the cycle is irregular only.

Sharman found that the first post-ovular menstruation in his lactating patients was at 13 weeks, but he found evidence of ovulation unrelated to a period in a similar case as early as seven weeks post-partum. He found none of the menstruations occurring within six weeks of a birth to be ovular in type. One would think therefore that pregnancy is not so likely in this patient, although it is still possible.

The biological pregnancy tests are unaffected by lactation and therefore can be used as accessory help in diagnosis.

KENNETH BOWES, M.D., M.S., F.R.C.S., F.R.C.O.G.

Treatment for 'Itching Ear'

QUERY.—Some patients who have been treated for the acute phase of otitis externa are left with an 'itchy ear' which is liable to flare up again. What can be done to relieve the itching, apart from treating the dandruff and banning cotton-wool?

REPLY.—Intolerable itching of the external auditory meatus is almost always relieved by the application of very small quantities of 1% hydrocortisone ointment. It is important that the ear should not be rubbed, and water must not be allowed to enter the meatus.

The following cream is also useful in relieving the itching sensation in the ear:—

Ichthyol	10 minims (0.6 ml.)
Cream of zinc oxide, B.P.C. ..	1 ounce (28.5 g.)

Only a very little should be painted in the ear and the application should be confined to the outer part of the meatus.

W. A. MILL, M.S., F.R.C.S.

T.A.B. Inoculation in Infants

QUERY.—At what age may a young baby proceeding to the tropics be given T.A.B. What is the dose?

May T.A.B. be administered during the six weeks following BCG inoculation?

What is the reason for withholding cholera vaccine from children under the age of 2 years?

REPLY.—Inoculations of T.A.B. vaccine do not appear to be necessary for babies under one year, at which period typhoid and paratyphoid infections are rare, and usually mild and atypical. The dosage of vaccine for young children is arbitrary and has probably been unduly cautious in the past. The British Army prepares a specially diluted vaccine for children, but even full-strength vaccine has been well tolerated in three doses of 0.1 ml. in the second year of life. The intervals are the same as in adult immunization.

As little is known concerning interference between T.A.B. and BCG, it might be wise to separate the inoculations by six weeks, whenever possible.

Children under one year (*not* those 'under the age of two years') are not immunized against cholera by the British Army authorities, because the risk of contracting the infection is less in the young child than in older children and adults. However, there is no reason why young babies should not be injected if desired. Reactions to cholera vaccination are usually negligible at all ages.

H. J. PARISH, M.D., F.R.C.P.ED.

European Children in Singapore

QUERY.—I have read the article on 'Bringing up European Children in S.E. Asia' (*The Practitioner*, December 1955, p. 714) with much interest. Would you kindly tell me whether this applies equally to Singapore, or is the climate

there less trying than in India? The reason why I ask is that I may be taking up an appointment in Singapore, but the fact that I have three children, aged 9, 7 and 4 years, makes me a little doubtful. In addition, one of my children has allergic rhinitis with occasional bronchospasm when affected with a common cold, but is by no means an established asthmatic in the true sense of the word.

REPLY.—This query is best answered by quoting from the 'Vital Statistics of Singapore Island relating to Europeans, 1954':—

Total Europeans ..	17,122	Death rate	6.25
Births	889	Birth rate	51.92

Infant mortality: 21.37 (including neonatal deaths)
Deaths of European children between 1 year and 19 years: 3
The climate is humid: Average maximum temperature, 86; average minimum temperature, 75.

There is no very dry hot season as in India, so it is not considered necessary for European children to go to hill stations and they can keep physically fit to any age. Malaria is now a rare disease—only 123 cases in 1954 out of 60,000 admissions to hospital.

As elsewhere in the East, the children's food and general hygiene should be supervised by the mother. The children will require vaccination against smallpox, and immunization against diphtheria and the enteric fevers is advisable.

With regard to allergy, the reaction of an individual cannot be predicted but, so far as I am aware, allergic manifestations are no more frequent in Europeans in Singapore than in a comparable group of well-fed people in this country. Many who suffer from hay fever in this country are free from it in Singapore, but of course the opposite can also apply.

R. BRUNEL HAWES, C.M.G., M.B., F.R.C.P.

PRACTICAL NOTES

Management of Cerebrovascular Accidents

THE importance of maintaining an open airway in a patient who is deeply unconscious following a cerebrovascular accident is stressed by John H. Hunt (*Proceedings of the Royal Society of Medicine*, March 1956, **49**, 170). Aspiration of mucus from the throat must be carried out frequently. He has found an electric sucker, which may be hired from one of the pharmaceutical firms, useful for this purpose. The patient is best nursed with the head on one or two pillows and over to one side, the paralysed side being upwards. 'The bowels can usually be left alone for a few days, and then an enema is better than a purge'. He 'nearly always' uses penicillin prophylactically to prevent the development of pneumonia, and streptomycin to prevent urinary infection, given in a combined preparation known as 'crystamycin'. Intravenous anticonvulsants may be required for convulsions, oxygen for cyanosis, venesection if the blood pressure is unduly high, and atropine for pulmonary œdema. To prevent painful stiffness later, the shoulder and other joints should be put through a full range of movements once a day. Lumbar puncture 'may relieve intracranial pressure better than anything else; it is seldom dangerous in these conditions if a fine needle is used, and the fluid drawn off slowly'. To maintain adequate hydration, he recommends feeding by a nasal tube: 3 to 4 pints (1.5 to 2.5 litres) of fluid, containing at least 2,500 calories, daily in small amounts at a time. 'An easy way to do this, and an easy one to remember, is to put down the tube every twenty-four hours, 4 pints of milk, 4 eggs, 4 ounces of sugar, the juice of 4 oranges, and 4 saltspoonfuls of salt, with what additional vitamins, antibiotics, sedatives, purgatives or other medicaments (such as digitalis if there is auricular fibrillation) may be required'. He has been impressed by the action of vitamin P in reducing the incidence of spontaneous subcutaneous ecchymoses in old people, and 'quite empirically' gives this vitamin to all his patients with strokes.

Paget's Disease of the Nipple

A SERIES of 27 cases of Paget's disease of the nipple is analysed by Percy Helman and Murray Kliman (*British Journal of Surgery*, March 1956, **43**, 481). Fifteen of the patients presented with eczema and superficial ulceration of the nipple only; 11 with a palpable lump as well as eczema, and one with a palpable lump of two months' duration and no obvious skin lesion. The patients reported that they first noticed an 'irritation' or 'itching' of the nipple, followed by scaling and crusting going on to a weeping stage which would often soil the clothes. The lesion always involved the nipple and areola and often spread to the skin of the breast, but in no case was a blood-stained discharge noted. Of the 15 patients in whom only the nipple lesion was found, four had a radical mastectomy (one with postoperative radiation), eight had local mastectomy (three with postoperative radiation), and three had biopsy excision plus postoperative radiation. One of these patients died of congestive heart failure, and one died from secondary carcinoma thirty-four months after a radical mastectomy. All the others are

alive and well after periods ranging from three months to seventeen years. Of the 12 patients with a palpable lump, nine had radical mastectomy (six with postoperative radiation), one had local mastectomy plus postoperative radiation, one had biopsy excision with postoperative radiation, and one had deep x-ray therapy. Ten of these patients are dead, one has carcinoma of the other breast, and the other is well but has only been followed for six months. Seven patients died within three years, and nine within five years. Experience in this series suggests that the length of the history of eczema does not appear to be of great prognostic import. The prognosis seems to be bad only in those cases with a palpable tumour of the breast, and it is suggested that local mastectomy followed by a course of deep x-ray therapy 'would seem a reasonable procedure for palliation at this late stage'.

Elimination of the Post-Partum Enema

'THE routine post-partum enema can be relegated to infrequent use in post-partum management', according to C. Donald Kuntze (*American Journal of Obstetrics and Gynecology*, April 1956, **71**, 893). His alternative method is to give an ounce (28.5 ml.) of mineral oil on the second post-partum evening. The following morning, if no evacuation has occurred, two ordinary glycerin suppositories are inserted into the rectum. If no bowel movement takes place within an hour, another suppository is inserted. This routine is repeated the following morning if no bowel movement has occurred in the interval, but this is seldom necessary. As an auxiliary measure the patient is encouraged to drink plenty of fluids. In a series of 100 consecutive obstetric patients, this procedure produced a spontaneous bowel movement in 88 cases. The twelve failures consisted of six nurses, all primiparas, and six multiparas 'in whose minds possibly the idea of routine post-partum enemas has been too firmly fixed and conditioned'. It is suggested that in non-nursing patients the additional use of a mild laxative, such as magnesium hydroxide, might further improve the results.

Chlorpromazine and Reserpine in Psychiatry

CHLORPROMAZINE and reserpine 'have changed psychiatric treatment greatly in the last two years', according to M. D. Altschule (*New England Journal of Medicine*, March 15, 1956, **254**, 515). On present evidence their 'chief value in therapy is that they produce conditions favourable to recovery in acute, self-limited psychoses, ameliorate anxiety in many syndromes and make behaviour, if not thinking, more nearly normal in chronic psychoses'. Chlorpromazine is the drug of choice in syndromes characterized by depression accompanied by extreme agitation. In these cases it is given intramuscularly for a few days and then orally. It is also of value in patients with severe recurrent anxiety, 'most' of whom 'report lasting benefit when given moderate doses by mouth'. Either drug, given parenterally, is of value in the treatment of delirium tremens and of the acute anxiety exhibited by addicts deprived of narcotic and barbiturate drugs.

Patients with senile psychoses, chronic schizophrenia or manic psychoses or with severe behaviour disorders, 'in whom destructiveness, assaultiveness, aggressiveness and noisiness constitute therapeutic problems, often show improvement of these symptoms when given chlorpromazine or reserpine'. Which drug should be used in a given case can only be decided by trial and error. The use of electroshock treatment is said to be reduced by 75%, and that of lobotomy by 100%. On the other hand, no more than 15% or 20% of these patients can be discharged from hospital: their delusions, and often their hallucinations, persist, but their behaviour is much improved. Jaundice, which occurs in about 1.5% of patients on large oral doses, is the only serious complication of chlorpromazine, and it usually disappears quickly when the drug is withdrawn. Perforation of gastric ulcers has been reported following the use of large doses of reserpine.

Treatment of Anorexia by Reserpine

THAT reserpine may be of value in helping underweight patients to regain weight is suggested by J. Durlach (*Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris*, 1956, **72**, 165). In a series of 10 such patients, all gained weight following the administration of reserpine, and half of them came up to the normal weight for their height and age. The usual dose he gave was 0.25 mg. thrice daily. The increase in weight was rapid, but there was not necessarily any direct correlation between increase in appetite and gain in weight. The time taken to gain the optimum weight varied considerably. Neither was there any constant effect noted on stopping treatment. Thus, in one case there was no fall in weight when reserpine was withdrawn, but in most cases the weight fell again when treatment was stopped. It is suggested that this effect of reserpine upon the weight is due to a direct effect on the di-

encephalon. The possibility is mentioned of reserpine being useful in the treatment of anorexia in mental patients.

Anxiety and Phlebitis

ACCORDING to Ph. Détrie (*La Presse Médicale*, March 17, 1956, **64**, 503), when a patient with thrombophlebitis complains of an otherwise inexplicable sense of anxiety, the possibility of an imminent venous thrombosis should be considered. In such a patient in whom venous thrombosis is known to have occurred, the onset of this symptom suggests a further thrombosis or the risk of an embolic accident. Two possible explanations of this sense of anxiety are put forward. One is that it is the result of stimulation of the sympathetic nerve endings in the wall of the affected vein. The other is that it is due to multiple minute pulmonary emboli. Whatever the cause, it is recommended that the onset of this sense of anxiety should be taken as an indication for the immediate institution of anticoagulant therapy. In the case of the patient already undergoing such therapy for venous thrombosis, it is an indication either that the dosage is inadequate, or that anticoagulant therapy is not controlling the thrombotic process and that other measures, such as venous ligation, may need to be considered.

A Silicone Barrier Cream in the Prevention of Bedsores

THE use of silicone vasogen ('lactagol'), which consists of 20% polydimethylsiloxane, in place of the usual routine treatment for the prevention of bedsores in elderly bedridden patients in a geriatric unit resulted in a lower incidence of fresh bedsores and a saving of ten minutes in the time spent daily on each patient by the nursing staff, according to F. J. A. Bateman (*British Medical Journal*, March 10, 1956, **i**, 554). The following procedure was employed over a period of six months for each of the 40 completely bedridden patients in a geriatric unit of 120 beds. Silicone vasogen was smeared thinly and evenly on pressure areas twice daily for a week, then once daily; the position of the patient was changed at least five times daily; the skin was washed with soap and water as infrequently as possible—pressure areas were washed only twice a week, or whenever they became fouled, and then only with warm water, followed by careful drying. This washing does not remove the silicone cream. All patients were given 25 mg. of tolazoline and 50 mg. of vitamin C three times daily. Established bedsores were treated on orthodox lines, but silicone vasogen was applied to the surrounding whole skin.

Saccharin and Cyclamates

IN a recent report the Council on Food and Nutrition of the American Medical Association (*Journal of the American Medical Association*, March 10, 1956, **160**, 875) summarizes the findings of the Food Protection Committee of the National Research Council on artificial sweeteners. These investigations show that 'there is no evidence that the use of nonnutritive sweeteners, saccharin and cyclamates ['sucaryl' is sodium cyclamate], for special dietary purposes, is hazardous'. On the other hand, 'knowledge of and experience with the use of cyclamates [which were introduced as sweeteners in 1950] are more limited than they are with saccharin', and it is recommended that further investigations should be made into, for instance, the minimum laxative dose of cyclamates in children. It is pointed out that knowledge of the mechanism of excretion of the cyclamates is incomplete, and 'considerations that may be of importance to their use in pregnancy, lactation, colonic conditions, or instances of renal dysfunction are incompletely known'. 'Continued observation of persons using cyclamate' is considered 'desirable'. The Council concludes that 'this valuable report [of the Food Protection Committee] gives a reassuring appraisal of the safety of these sweeteners for special dietary purposes but does not support the unrestricted use of these sweeteners in general purpose foods and beverages'.

Footwear for the Elderly Deformed Foot

BECAUSE of the state of their feet, many elderly people are unable to wear conventional footwear. This state of affairs may be remedied by chiropody or by the wearing of 'surgical footwear'. To provide an efficient national chiropody service for the whole country to cope with the increasing number of old people, however, is almost impossible, and 'surgical footwear' is expensive and inclined to be too heavy. To deal with this situation, J. Gordon Macdonald and H. K. Nandlal (*The Chiropodist*, April 1956, **11**, 113) describe a method of making footwear which can be used in clinics and hospitals—and by enterprising general practitioners. The technique has been successfully used in several general hospitals in London, and is equally adaptable for younger arthritic patients with deformed feet. Full details are given of how to make the footwear, which consists essentially of a sponge-rubber sole, whilst the uppers are made of strapping covered with latex. Although the finished product is neither elegant nor permanent, it is comfortable and is simply and quickly made of cheap materials.

REVIEWS OF BOOKS

The Practice of Medicine. EDITED BY JOHN S. RICHARDSON, M.V.O., M.D., F.R.C.P. London: J. & A. Churchill Ltd., 1956. Pp. viii and 1076. Figures 67. Price 40*s*.

THIS new textbook of medicine may not unfairly be described as London's reply to Edinburgh and the provinces. It is the third book of its kind to make its appearance in this country since the end of the 1939-45 War. Of its two predecessors, one was almost entirely written by the staff of the provincial medical schools, whilst the second was an Edinburgh product. Dr. Richardson's is practically a St. Thomas's-St. Bartholomew's product, all but three of the 14 contributors coming from these two ancient institutions.

Let it be said right away that this is an excellent textbook of medicine, which can be thoroughly recommended to the undergraduate as a companion to his clinical studies. It has certain unusual features. The introductory chapter, on 'The nature of disease', is written by a psychiatrist, whilst that on 'Immunity and allergy' is by a dermatologist. Diseases of the skin as such are not included, but a dermatologist contributes chapters on sarcoidosis, and the collagen diseases. The contributors include a general practitioner, who is joint-author of the concluding chapter on 'The management of terminal disease'. The only criticism that is called for concerns the scant attention paid to the alimentary tract, which is dismissed in 17 pages, with a further 16 pages on the liver and pancreas. This compares with 154 pages devoted to the central nervous system and 146 pages to psychiatry. In view of the small amount of space allotted to him, it is not surprising that the author has not been able to do justice to diseases of the alimentary tract. This, however, does not justify the statement that 'sodium bicarbonate, a teaspoonful stirred in a little warm water, is probably the most effective' alkali in the treatment of peptic ulcer.

This is a notable addition to the hierarchy of textbooks of medicine, and will undoubtedly meet the needs of many generations of medical students. Not the least of its attractions is the commendably low price at which the publishers have been able to make it available.

Diseases of the Chest. BY H. CORWIN HINSHAW, M.D., and L. HENRY GARLAND, M.B., B.CH. Philadelphia and London: W. B. Saunders Co., 1956. Pp. x and 727. Figures 288. Price £5 5*s*.

THIS book has been written by a physician and a radiologist to provide an up-to-date account for students and practitioners of 'most of the thoracic disorders which they are likely to encounter in practice'. After four introductory chapters on diagnostic methods in which the fallibility of clinical and radiological diagnosis is emphasized, the various diseases of the chest are considered seriatim. The clinical and radiological descriptions are admirable but the pathological sections in each chapter are brief, and occasionally the physiological interpretations of symptoms are questionable. The radiological illustrations are of high quality, and are accompanied in most instances by case summaries which are most instructive. In some sections the account of general manifestations of thoracic diseases is rather scanty: for instance, the frequency with which lung cancer presents through secondary deposits in other organs, and the renal complications of sarcoidosis are hardly mentioned. It is interesting to note ways in which American views and practice differ from our own. Thus, chronic bronchitis is regarded as an infrequent condition whose diagnosis is to be shunned, and most cases so diagnosed are considered to be 'victims of asthma, emphysema, heart failure, bronchiectasis, tuberculosis, pneumonia and other diseases in which bronchitis is but a minor component of the disease'. Streptomycin-dihydrostreptomycin mixtures are recommended as routine in tuberculous therapy and there is rather more emphasis on collapse and surgical therapy than would generally be given in this country. Naturally there are full accounts of diseases such as histoplasmosis and coccidioidomycosis which we seldom encounter. There are good references, often with useful commentaries, chiefly to recent American literature, and exhaustive differential diagnostic lists (e.g. 43 causes of pleural effusion and 89 differentials for pulmonary tuberculosis).

This book is a most useful addition to the literature on chest diseases, both in respect of the help it will provide for the clinician and as a guide to the literature. It is probably the best textbook on the subject available today.

Diseases of the Thyroid Gland. BY SAMUEL L. CARGILL, M.D., and MARK FALCON LESSES, M.D. Oxford University Press. London: Cumberlege, 1955. Pp. vii and 490. Illustrated. Price 90*s*.

IF, at any rate to its author, an unduly long time seems to have passed between the issue of this book last August and the appearance of this

review, the delay may be ascribed to the fact that the reviewer was sufficiently interested to read it. It is an enjoyable and salutary thing for one not altogether inexperienced in thyroid disorder to sit back and examine in a friendly but critical way the fruits of the experience of twenty-five years in the life of the endocrine clinic of the Beth Israel Hospital. It must be, surely, the father of endocrine clinics, and, in thyroid disease, its experience covers the age of stable iodine, to which the authors have not yet lost their allegiance, the age of the antithyroid drugs, in which they appear to have lost interest a little, since they do not mention carbimazole, and the present age of radioactive iodine, in the use of which they follow the cautious methods to which we are accustomed in England.

In the introductory words of Dr. Means, the book is comprehensive, meticulous and well arranged. The whole subject is dealt with in a well-balanced way. The mistakes which do not permit of argument are few, though 'papilliferrous' tumours are not related to the metabolism of iron, and myxœdema and hypothyroidism are not synonymous. Perhaps, too, we are getting a little tired of Sir Charles Harington's Mrs. S., who has now been advertising the benefits of thyroid therapy in myxœdema from textbook to textbook for almost as long as the life-span of the Beth Israel clinic.

I. P. Pavlov. Selected Works. Moscow: Foreign Languages Publishing House, 1955. Pp. 654. Price 10*s.* 6*d.*

THIS is a fascinating book and very good value. It is published with the imprimatur of the U.S.S.R. The ideological obligato that runs through the introduction and textual commentary is amusing to a Western reader but allowance is readily made for this obsessive thinking, for it is an admirable production of Pavlov's works and the annotations are mostly factual and helpful.

Pavlov believed that, because of the oneness of the animal organism needing endless adaptations to a hostile environment, the laws governing the fixed and inborn reflexes in and below the diencephalon must also govern the acquired and conditioned reflexes of the cerebral cortex. It is curious that Sherrington did not admit the validity of his ideas. This was evidently a very sore point with Pavlov. He records that Sherrington once said to him 'Your conditioned reflexes will never be popular in England since they have a materialistic flavour'. Actually, Pavlov's attitude to science was that of all the great masters: he believed that science was only concerned with facts and not with speculations beyond them. In 1909 he told a congress of Russian physicians that he did not deny the existence of an inner world of the human being and 'even less am I inclined to deny anything which concerns the deepest aspirations of the human spirit'. One may wonder how this declaration of faith in a world beyond our ken can be fitted in with dialectical materialism. Perhaps Pavlov wondered too.

Psychiatry for the Family Physician. BY C. KNIGHT ALDRICH, M.D. New York and London: McGraw-Hill Publishing Co. Ltd., 1955. Pp. ix and 276. Price 43*s.*

FAMILY physicians are divided into two main classes: those who are irritated by patients suffering from personality disorders and emotional disabilities (useful labels which cut out psychiatric jargon), and those who realize that sickness affects the whole man, body, mind and spirit. The former will not be inclined to buy this book anyway; the latter will want to read it because it gives one of the clearest expositions the reviewer has read of the orthodox psycho-dynamic points of view and yet includes recent work, especially from the American schools. The author uses in many cases simple phrases that describe the anomalies of human nature in clear understandable terms. His diagrams on unconscious mental processes are new and refreshingly clear. All the various psychological difficulties from which the average patient suffers are covered. Guidance of married couples with personality problems is especially helpful. The author is careful to set the limits beyond which the non-specialist cannot go. Many readers will think that the limits are too wide, but after ten years of family practice the reviewer feels that the book will lead to a greater capacity for the family physician to treat personality disorders in their early stages, and so act as a valuable contribution to preventive medicine.

Etiology of Chronic Alcoholism. EDITED BY OSKAR DIETHELM, M.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications, 1955. Pp. 229. Figures 10. Price 50*s.*

ONE becomes increasingly aware of the complexity of the study of the subject on reading this symposium. The problems are tackled by various authors with all the intensity and sincerity of modern American scientific approach, with a rather dull European contribution of the constitutional background of Swiss and American alcoholic patients by Bleuler. One could point out that the psychiatric material of a selected group of upper-class American alcoholics,

comprising fifty patients, is hardly a fair sample of American alcoholism, and that the proportion of psychotic personalities reported in the psychopathological studies is probably excessive. That alcoholism is an illness which needs psychiatric treatment and should be assessed solely on an individual approach is a conclusion with which one must agree wholeheartedly. A fascinating chapter by Fleetwood on the biochemical investigations of emotions, with the presence in the blood not only of noradrenaline, but of a separate 'tension substance' and a 'resentment substance' particularly in alcoholic patients, with the striking specific effect of alcohol on the 'resentment factor' opens a new field not only in the pharmacological but in the psychotherapeutic attack on the chronic alcoholic. The material is broadly based, from chapters on the physiological, psychological and genetic aspects; and has even an anthropological study of alcoholic behaviour patterns in a selected community.

This book, although restricted in scope, is well worth further study, and may offer much light on how to stimulate further research on this vital problem of today.

Praktische Diagnostik in der Unfallchirurgie. By Dr. Erhard Ahrer. Vienna: Urban & Schwarzenberg, 1955. Pp. xi and 151. Figures 168. Price S159; DM 26.50.

This is a quite excellent little book for the guidance of the general practitioner. It deals most sensibly with the problems for which the general practitioner himself can take responsibility, and it gives clear instructions upon which cases should be sent to the accident service of the local hospital. The whole subject of accident surgery is condensed into an extremely well-produced little book. Crisp and accurate descriptions of the clinical appearances of common injuries are given, and this includes not only fractures and dislocations, but also the cerebral complications of fractures of the skull. There is a section dealing with shock, the general principles of plaster technique, and the initial treatment of open wounds.

Nervousness, Indigestion and Pain. By Walter C. Alvarez, M.D. London: Staples Press Ltd., 1956. Pp. 250. Price 15*s*.

This is a brilliant book, full of wisdom, insight and common sense. For years it has stood as a rock in the mælstrom formed by the meeting of the foaming torrent of soma-chemistry and the turgid undertow of psycho-bilge. It is indeed, as the publishers claim, a classic of American medicine. This edition is a 'popular' one, and the book 'has been rewritten in simple speech in order to help those many persons with nervousness, indigestion, and pain who would like to learn more about their personal problems of illness than their physicians have time to teach'.

From this rewriting Dr. Alvarez emerges, like Lamb's Coleridge, as 'an archangel a little damaged'. The clear exposition, simple style, and illuminating anecdotes all remain; but the level of thought and sweep of ground covered are rather too much for most laymen. The deceptive simplicity is prone to engender new, rather than cure old, neurosis. Nevertheless, integrity and sincerity are evident on every page; and the reader is unlikely ever to develop that malady known as Bumpsterhausen's blue follicles.

Obstetrics and Gynæcology for Nurses. By Gordon W. Garland, M.D., M.R.C.O.G., and Joan M. E. Quixley, S.R.N. London: English Universities Press Ltd., 1956. Pp. xii and 188. Figures 58. Price 10*s*. 6*d*.

This book is one of a series, the aim of which is to provide a range of textbooks for students of nursing. This particular contribution is intended for the student nurse studying for her S.R.N. certificate. Starting with a short glossary of terms used, the authors deal with the anatomy of the female genital tract and then continue with the normal cycle of menstruation, pregnancy, labour and the puerperium in a delightfully simple and clear way. Following this, abnormal pregnancy is considered and then gynæcological disorders. Nursing care and treatment are described throughout. Finally the work of the gynæcological outpatient department is outlined, and the care of the patient before and after the various gynæcological operations. There is little doubt that this concise book, which is well illustrated, will be welcomed.

NEW EDITIONS

A Short Practice of Surgery, by Hamilton Bailey, F.R.C.S., F.A.C.S., and R. J. McNeill Love, M.S., F.R.C.S., F.A.C.S., in its tenth edition (H. K. Lewis & Co. Ltd., £4 4*s*.), will maintain its reputation as the most readable book in surgery. It keeps the atmosphere of breathless and excited concentration, the copious illustrations, and the flair for apt summary, that have made it so attractive to students. The authors have grasped the fact, fundamental in education, that most men think in pictures and remember pictorially, so that, however easily they may understand a written paragraph, they remember it better if a simple

illustration accompanies the text. In one way only does it mislead—it is no longer short. It has more than a thousand pages, larger pages than before, with illustrations, often several, on every page. At four guineas, it is wonderful value.

Textbook of Endocrinology, edited by Robert H. Williams, M.D., second edition (W. B. Saunders Co., 91s.).—This outstanding book is written by ten eminent American contributors who have had wide experience in clinical and laboratory endocrinology. There are descriptions of the newest hormone preparations, including fluorohydrocortisone, prednisone and triiodothyronine, and discussions on the use of hormones in treating diseases such as mammary and prostatic carcinoma, collagen diseases and allergic conditions. The chapters are uniformly of a high order and a vast amount of information is concisely and lucidly given. In addition to the clinical and laboratory features of endocrine disorders the physiology of each gland is fully described, but in some cases a more detailed description of the clinical pictures could have been given. Reference to the Hand-Schüller-Christian syndrome is omitted and there is no mention of the nicotine test for diabetes insipidus. It would have been helpful if the doses of progesterone and œstrogen used in habitual abortion had been given. Some of the terms employed may come as a minor shock to the average British reader, such as, thyroxinopenia, dipsosis, edemagenesis, radioiodotherapeusis of thyrotoxicosis, polygalactodipsia.

This book can be strongly recommended to physicians and endocrinologists as a comprehensive and up-to-date work.

Midwifery, by R. Christie Brown, M.B., M.S., F.R.C.S., F.R.C.O.G., Barton Gilbert, M.D., F.R.C.S., F.R.C.O.G., Donald B. Fraser, B.M., B.CH., F.R.C.S., F.R.C.O.G., and Richard H. Dobbs, M.D., F.R.C.P., fourth edition (Edward Arnold (Publishers) Ltd., 25s.).—The continued success of Christie Brown's 'Midwifery' is a tribute to the work and teaching of the City of London Maternity Hospital, to which its four authors, Mr. Donald Fraser being a new contributor, are attached. The text covers the whole range of midwifery practice and not only meets all the requirements of pupils studying for the examinations of the Central Midwives Board, but also the needs of all those—doctors, dressers, and midwives alike—who are charged with the responsibility of the care of pregnant women, yet do not profess to be obstetric specialists. In addition, the basic facts of biology, of human anatomy and human physiology are described lucidly and in sufficient detail to ensure that a midwife can develop her experience throughout her career and not only until she qualifies: an important quality in a textbook such as this if midwifery is to maintain its status as a skilled profession. The authors and their publishers are to be congratulated on a valuable contribution to the literature of their subject.

Elements of Healthful Living, by Harold S. Diehl, M.D., Sc.D., in its third edition (McGraw-Hill Publishing Co. Ltd., 34s. 6d.), is an improvement on an already excellent book. It is a straightforward statement of the known facts about health, written without exaggeration or overstatement in clear and concise English, for the American student. It contains 17 chapters: the importance and the possibilities of better health; our major health problems; mental health; nutrition and growth; the choice of foods; digestive disturbances; stimulants and narcotics; exercise—fatigue—rest; specific disease prevention; care of the nose, throat, ears, and teeth; the conservation of vision; care of the skin and hair; sex life; modern parenthood; problems of advancing years; choosing a health advisor; community health. It would make excellent reading for teachers as a source of health education material in secondary schools.

Medical Photography, by T. A. Longmore, HON.F.S.R., in its fifth edition (Focal Press, 60s.), will be welcomed by all called upon to practise medical photography and radiography. The new edition contains an excellent section on colour photography which has been extensively revised and enlarged. Covering as it does such a wide range, this book is essential to the library of any x-ray or photographic department as a valuable book of reference. The illustrations are of good quality and the numerous diagrams are clear and a valuable asset to the book. There is a useful appendix containing full formulary for developers, replenishers, and the like, and a useful glossary of terms.

INDEX AND BINDING CASES

The index to Vol. 176 (Jan.-June, 1956) will be forwarded to all subscribers with the July 1956 issue. Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 5s. 6d. each, post free. The cases are made to hold 6 copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 13s. 6d. per volume; this includes the cost of binding case and return postage.

The contents of the July issue, which will contain a symposium on 'Home Care and Nursing', will be found on page civ at the end of the advertisement section.

Notes and Preparations, see page 703
Fifty Years Ago, see page 707
Motoring Notes, see page lxxxvii

DRAMAMINE* IN VERTIGO

Labyrinthine Disturbance

Long recognised as a standard for the management of motion sickness, Dramamine has become accepted in the control of a variety of other clinical conditions characterised by vertigo.

Vertigo, it has been claimed†, is primarily due to a disturbance of those organs of the body that are responsible for body balance. When the posture of the head is changed, the gelatinous substance in the semi-circular canals begins to flow. This flow initiates neural impulses which are transmitted to the vestibular nuclei. From this point impulses are sent to different parts of the body to cause the symptom complex of vertigo.

Some impulses reach the eye muscles and cause nystagmus ; some reach the cerebellum and skeletal muscles and righting of the head results ; others activate the emetic centre to result in nausea, while still others reach the cerebrum making the person aware of his disturbed equilibrium. *Vertigo may be caused by a disease or abnormal stimuli of any of these tissues involved in the transmission of the vertigo impulse, including the cerebellum and the end organs.*

A possible explanation of Dramamine's action is that it depresses the overstimulated labyrinthine structure of the inner ear. Depression, therefore, takes place at the point at which these impulses, causing vertigo, nausea and similar disturbances, originate. Some investigators have suggested that Dramamine may have an additional sedative effect on the central nervous system.

Repeated clinical studies have established Dramamine as valuable in the control of the symptoms of Ménière's syndrome, radiation sickness, hypertension vertigo, the vertigo of fenestration procedures, labyrinthitis and vestibular dysfunction associated with antibiotic therapy, as well as in motion sickness.

Any of these conditions in which Dramamine is effective may be classed as "disease or abnormal stimuli"† of the tissues including the end organs (gastro-intestinal tract, eyes) and their nerve pathways to the labyrinth.

The site of Dramamine's action is probably in the labyrinthine structure.

Dramamine (brand of dimenhydrinate) is supplied in tablets of 50 mg. in bottles of 12, 36, 100 and 1000 tablets and cartons (10 strips of 10 tablets). G. D. Searle & Co., Ltd., 83, Crawford Street, London, W.1.

SEARLE

*Regd. Trade Mark

†"Dizziness": Vertigo and Syncope, GP 8:35 Nov.) 1953.

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ANTI-ALLERGIC AND DECONGESTANT

IMMEDIATE RELIEF IN HAY FEVER AND

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Prolonged freedom from symptoms

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14/5

NOTES AND PREPARATIONS

NEW PREPARATIONS

'BIOFERGATE B' tablets each contain 5 grains (0.3 g.) of ferrous gluconate B.P.C., and 1 grain (60 mg.) of aneurine hydrochloride B.P. Issued in bottles of 250 and dispensing packs of 1000. Also available as an elixir containing 0.3 g. of ferrous gluconate B.P.C., 1 mg. of aneurine hydrochloride B.P., 1 mg. of riboflavine and 10 mg. of nicotinamide B.P., with traces of copper and manganese, per teaspoonful. Issued in bottles containing 8 and 80 fluid ounces. (Biorex Laboratories Ltd., 47/51 Exmouth Street, Rosebery Avenue, London, E.C.1.)

'BIORUB' is a preparation for topical application in cases of 'rheumatic pain, muscular pain of traumatic origin', and neuritic pain. The constituents are: methyl nicotinate, 1%; glycol salicylate, 10%; histamine dihydrochloride, 0.1%; and capsicin B.P.C., 0.1%. Issued in packs of 2 ounces and in dispensing packs of 2 kg. and 1 lb. (Biorex Laboratories Ltd., 47/51 Exmouth Street, Rosebery Avenue, London, E.C.1.)

'MERATRAN' tablets each contain 1 mg. of pipradol hydrochloride, and are intended for the treatment of 'depression and fatigue states'. Tablets containing, in addition, 0.25 mg. of reserpine ('meratran with reserpine') are also available for patients suffering from depression where agitation is also present. Both preparations are issued in bottles containing 30, 100 and 500 tablets. (Riker Laboratories Ltd., Morley Street, Loughborough, Leicestershire.)

PHARMACEUTICAL NOTES

BOOTS PURE DRUG CO. LTD. announce the introduction of 'streptoduocin viules' (stabilized injection of streptomycin and dihydrostreptomycin), each containing 2 ml. of stabilized solution equivalent to 0.5 g. of streptomycin and 0.5 g. of dihydrostreptomycin as sulphates. Available in packs of 6 and 100. (Station Street, Nottingham.)

THE DISTILLERS CO. (BIOCHEMICALS) LTD. announce that their preparation of crystalline penicillin G (sodium salt) will in future be marketed under the name 'Solupen'. Their preparation of crystalline penicillin G (potassium salt, buffered) will be known as 'Solupen' buffered. (Speke, Liverpool, 19.)

JOHNSON & JOHNSON (GT. BRITAIN) LTD. announce that they are now producing a porous elastic adhesive bandage. This consists of 'elastic cloth spread with self-adhesive plaster mass in such a way that pores of uncoated cloth are left, through which heat, water-vapour and skin-secretions may pass'. To help prevent the curling-up often caused by the friction of clothing, the plaster is spread to the very edge of the bandage. It 'does not macerate the skin, can be removed with little discomfort', and complies with the requirements for zinc oxide self-adhesive bandage B.P.C. Available in widths of 2½ and 3 inches by 5 to 6 yds. stretched. (Slough, Bucks.)

ROUSSEL LABORATORIES LTD. announce that their 'hydrocortisyl skin ointment' is now available in an additional strength (½ per cent.). Issued in tubes containing 5 g. and 15 g. (847 Harrow Road, London, N.W.10.)

TRUFOOD LTD. announce the addition of 'apricots with semolina' to their 'spoonfoods' range of strained and homogenized foods for infants. This 'has a definite fruit flavour but the sharpness of the apricots is softened by the blandness of the cereal, making it palatable to the young child'. (Green Bank, London, E.1.)

HUNTERIAN SOCIETY'S GOLD MEDAL ESSAY

THE subject for the Hunterian Society's Gold Medal essay this year is 'The care of the growing child in general practice'. The competition is open to all general practitioners. Further details may be obtained from the honorary secretary, Mr. R. S. Murley, 95 Harley Street, London, W.1.

FILM NEWS

Keep it Clean (16 mm., sound; running time 25 minutes) shows how lack of hot water in homes and restaurants can lead to the spread of infection. Available on free loan upon application to the Gas Council, 1 Grosvenor Place, London, S.W.1, or from local gas showrooms. Applications should be made at least fourteen days in advance of showing date.

Health Films.—The Ministry of Health list of selected health films, giving details of films available and facilities for hiring, has now been revised and may be obtained upon application to: The Central Film Library, Government Building, Bromyard Avenue, London, W.3; The Scottish Central Film Library, 16-17 Woodside Terrace, Charing Cross, Glasgow, C.3; or The Central Film Library of Wales, 42 Park Place, Cardiff.

NATIONAL SPASTICS SOCIETY

ON May 16, Miss Patricia Hornsby-Smith, M.P., performed the official opening ceremony of the

National Spastics Society's first residential treatment centre for adult spastics, at Prested Hall, Kelvedon, Essex. This centre for 30 men and women with cerebral palsy is the only residential centre of its kind designed to help adult spastics.

CHIROPODY FOR OLD PEOPLE

In their 8th annual report, for the year ended September 1955, the governors of the National Corporation for the Care of Old People announce that they have set aside the sum of £60,000 to be spent over a period of three years in making grants to voluntary organizations providing chiropody at reduced rates for old people whose circumstances do not permit them to pay the full rates for treatment. Owing to the limit of the funds available it is unlikely that grants will be made in those areas where financial assistance can be obtained from the local authority under the National Health Services Act.

A TONSILLECTOMY CENTRE

In July 1954, a 'tonsillectomy centre' was opened in Sheffield. Patients are received on Monday afternoon for operation on Tuesday morning and are discharged at noon on Wednesday. Another intake comes in on Wednesday afternoon for operation on Thursday and discharge on Friday. The maximum intake is 19 patients twice a week, and between July 1954 and March 1955, 1,092 operations had been performed. As a result of this new venture the waiting time for tonsillectomy has been reduced from two years or more to 16 weeks or less.

In reporting this innovation, the First Report of Sheffield No. 1 Hospital Management Committee, which covers the period July 1948 to March 1955, also gives details of a questionnaire which was sent to the parents of 200 of the children who had been operated on in the Centre. Of the 159 parents who replied, only seven said that their child did not like 'being put to sleep', whilst in 25 instances, after return home the child had said that he (she) did not like having his (her) tonsils taken out. None of the parents was critical of the treatment the children had received.

GRAMMAR SCHOOL FOR PHYSICALLY HANDICAPPED BOYS

The Ministry of Education announces that in September this year a special school for able and gifted physically handicapped boys will be opened in association with the Lord Mayor Treloar Training College, Froyle, near Alton, Hampshire. Boys will be admitted to the school at any time from the age of 11, and will receive full-time general education up to the age of 16, with some general introduction to technical work. At the age of 16 it will be possible to transfer to the vocational courses which are provided in the College. If there appears to be sufficient demand, it is hoped to develop more advanced academic courses for boys likely to profit from them. The school will have accommodation for about 70 boys, and applications for admission will be considered from any area in England or Wales. Applications and requests for further information should be made to The Warden, Lord Mayor Treloar College, Froyle, near Alton, Hants.

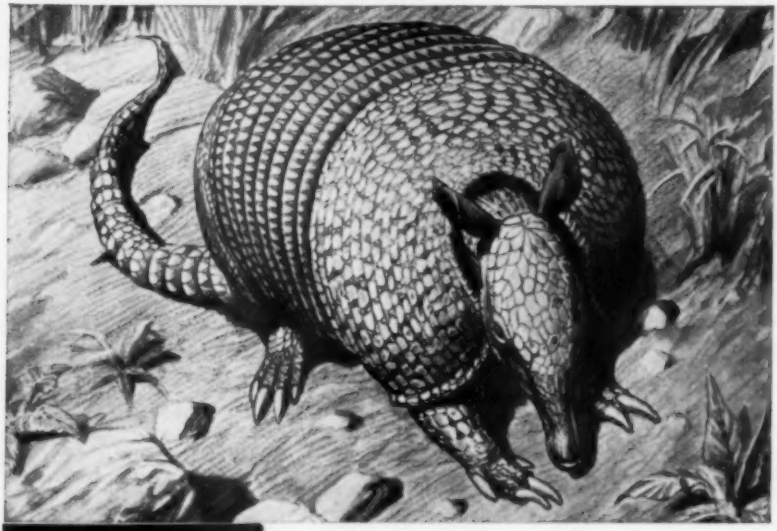
DIPHTHERIA IMMUNIZATION

The Ministry of Health has drawn attention to the fact that the aim of the diphtheria immunization campaign is to secure the immunization of not less than 75% of babies before their first birthday. In 1954, only 36% of such children were immunized, and in the first half of 1955 the number was only 38.4%. In recent years the fatality ratios in the younger age-groups—under 1 and 1-4—have remained high when compared with the other age-groups. It is feared that, unless the immunization of younger age-groups can be made more complete, the shift in the incidence of the disease to the 1-4 age-groups may become more pronounced—and this is the age at which diphtheria is most likely to be fatal.

LAUNDERING FOR THE TUBERCULOUS

According to the *NAPT Bulletin* (1956, **19**, 32), the practice with regard to tuberculous patients' laundry in British sanatoria and in hospitals with tuberculosis units 'varies greatly—from steam or other sterilization of all patients' and ward articles to a complete lack of any precautions'. Many hospitals make no arrangements for the patient's personal laundry. Soiled clothing is kept in the bedside locker until collected by a relative or friend who takes it away, 'probably in her shopping basket, and washes it at home—sometimes in a crowded house among young children'. Some of the larger sanatoria have their own laundries, with separate intake and sorting rooms for patients' and staff laundry and separate washing machines. All articles from the wards are handled as little as possible and the laundry staff wear masks and protective clothing. Other sanatoria have their own laundry but either make no attempt to separate the soiled linen or use methods which are obviously ineffectual. For instance, the staff laundry is washed first, and the patients' and ward articles in the same

CONTINUED ON PAGE 705



Nature's defences...

...for animals The Armadillo, a harmless inoffensive mammal, has a full measure of Nature's most predictable defences. Foremost is the remarkable rapidity with which it can burrow into the ground; next comes the speed with which it runs, despite its short legs; third, are its acute senses of smell and hearing; and last but not least, comes its characteristic protective armour which proves a powerful defence when the Armadillo rolls up hedgehog fashion.

...for humans Nature also provides predictable defences for man. In one of these—TERRAMYCIN, a broad-spectrum antibiotic derived from a tiny wrinkled mould found in the soil—she has provided man's most predictable means of defence against microbial attack. Effective in more than 100 infections, TERRAMYCIN with its rapid anti-microbial action and fewer side effects ensures a more positive defence against more organisms than any other anti-infective agent.

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machinery afterwards, but the equipment is not disinfected before the next washing of staff laundry.

CHINESE TÆNICIDES

ARECA nut and pumpkin seeds have both been removed from the *British Pharmaceutical Codex*—the former was deleted from the current edition and the latter from the 1949 edition. They are both, however, still widely used in China. Indeed, areca nut is found in anthelmintic prescriptions in old Chinese medical literature published twelve hundred years ago. L. C. Feng, of the Chinese Union Medical College, Peking (*Chin. med. J.*, 1956, **74**, 17) has investigated the combined use of these two preparations, and reports a cure rate of 95.15% in 96 cases of *T. saginata* infection. The results in *T. solium* were not so satisfactory: only eight out of 20 cases were cured by the combined therapy. He reports *in vitro* experiments which are said to show that the paralytic effect of pumpkin seed is on the middle and posterior parts of the worm, whilst areca nut acts on the scolex and anterior parts of the worm.

FLUORIDE AND DENTAL CARIES

A CONVINCING demonstration of the value of fluoride in the prevention of dental caries is provided by Miss Jean R. Forrest (*Brit. dent. J.*, 1956, **100**, 195), who has investigated the incidence of caries in four areas in England, in which fluoride occurs naturally in the water supplies at concentrations of 5.8, 3.5, 2.0, and 0.9 p.p.m. respectively. A group of 324 children aged 12 to 14 years in these fluoride areas (West Mersea, Burnham-on-Crouch, Harwich, and Slough) was compared with a comparable group of 259 children in Saffron Walden, and Stoneleigh and Malden West, where the drinking water contains only a trace of fluoride. In the fluoride areas the percentage of children free of caries ranged from 24 to 50, compared with only 4 to 8 in the non-fluoride areas. Even more striking was the absence of caries in the first permanent molars, generally considered to be the most vulnerable teeth in childhood. In the fluoride areas 59% to 76% of these teeth were entirely sound, compared with only 22% in the non-fluoride areas.

THE WELFARE STATE

THE following is an excerpt from a letter from a medical officer in Essex, which was published in a recent issue of *The Medical Officer* (1956, **95**, 112). One problem family 'in my area has had visits from the following during the last year or so: the police, the general practitioner, the almoner, the clinic doctor, myself, the health visitor, the N.S.P.C.C. inspector, the children's officer, the district nurse, the Ministry of Labour, the Assistance Board, the local housing department, the electricity authority, the D.A.O., the vicar, a voluntary society, the sanitary inspectors of three local authorities, plus various charitable neighbours'. The writer of the letter adds: 'When their child reaches school age I anticipate we shall be able to improve on this modest total of 20 workers in the field of social rehabilitation. The family I may add is quite "unspoilt" and unreformed by such attention'.

EXPERT EXPECTORATORS

THE practice of medicine in Africa has many unexpected complications for the Westerner. In an interesting article on 'health visiting in the Sudan' (*Nursing Times*, 1956, **52**, 102), Miss Evelyn E. Davies, a health visitor in Omdurman, comments on the universal habit of spitting in the Moslem world. This is accentuated during the Ramadan feast when no good Moslem may swallow anything between sunrise and sunset. As he is not even allowed to swallow his salivary secretions, he has no alternative but to expectorate. Miss Davies continues: 'They are clean spitters with an accurate aim and begin the practice early in life, so it is not uncommon for a child sitting in the middle of his class at school to turn his head towards the window, and over the heads of his class-mates make a perfect shot to the compound outside; it would, of course, be unlucky if anyone were passing, but otherwise nobody turns a hair, except perhaps the teacher if he happens to be a Westerner'.

A NEW USE FOR TELEVISION

A REPORT from the United States announces the installation in a hospital in New Jersey of a device whereby patients in the hospital can see their children by television and speak to them at the same time by telephone. The device, which operates for five minutes when a coin is put in a meter, enables patients to see and talk to children who are too young to visit the wards in person. It is a one-way vision device. The patient can see the visitor in a booth in the hospital, but the visitor cannot see the patient, but they can speak to each other.

AMPHETAMINE AS A DRUG OF ADDICTION

THE abuse of amphetamine and its derivatives has become a public health hazard in many countries, according to the WHO expert committee on drugs liable to produce addiction.

The problem appears to be particularly acute in Japan, where there are estimated to be 1.5 million people abusing the drug. These addicts usually administer the drug to themselves intravenously or subcutaneously. Of 60 murder cases in Japan in May and June 1954, 31 convicted murderers had some association with the misuse of amphetamine, or 'wake-amine' as it is popularly known. 'Wake-amine' addiction is said to have much to do with the prostitution and gambling prevalent in Japan since the end of the War.

PRESCRIBING OF SUPPOSITORIES

ACCORDING to the *Pharmaceutical Journal*, there has been an increase in the prescribing of suppositories in France. Colds, influenza and bronchitis are among the conditions being so treated, and aspirin is a common constituent of such suppositories. The 1956 catalogue of French specialities lists 200 different suppositories.

PUBLICATIONS

Talking with Patients, by Brian Bird, M.D.—This little book consists of thirty chapters, each of which deals with the art of talking to a particular class of patient or about one particular medical subject. A seasoned practitioner will find much of it an elucidation of the obvious, but the young doctor may well come across many a surprising fact which would normally take the rasp of time to turn to truth. The author is a psychiatrist and when he deserts common or garden sense and indulges in mere psychiatry the result is not so happy. For instance, chapter 23, 'example of reaction to injection', details the contrasted attitude of two boys to an injection: one was apparently nonchalant and polite and consequently had a headache and vomiting and was prostrate that evening; the other who did not repress his fears and made a terrible fuss was therefore perfectly happy thereafter. To suggest that this is an example and not a rare exception is contrary to what every practitioner, who almost daily does immunizations, knows. (Pitman Medical Publishing Co., price 24s.).

The Pocket Book of Diets, by G. Barry Carruthers, M.D., is one of a series of pocket books dealing with diverse subjects ranging from the law to rhododendron cultivation. The layman will learn from it the principles of nutrition and the rationale for the diets prescribed in different diseases. It contains much sound advice given in a clear and concise manner. The practitioner will find useful the details about different diets and the food values which are given. (Evans Brothers Ltd., price 5s.)

Memorandum on Immunological Procedures which Service Personnel and their Families may need at Home and Abroad is the second edition of the admirable little booklet first brought out by the War Office in 1952. It fully attains its object of providing 'in a composite form a ready reference of the present administrative and technical instructions relating to the types of immunization' required for Service personnel and their families, and can be thoroughly recommended to civilian practitioners as well as Service medical officers. (H.M. Stationery Office, price 2s. 6d.)

An Introduction to Pool Exercises by Elizabeth Bolton, M.C.S.P., H.T., and Diana Goodwin, M.C.S.P., H.T.—The value of pool bath treatment for disabled limbs is increasingly recognized; and a knowledge of it may soon be required of all physiotherapy students. They will find this an excellent textbook. A minimum of verbal description of remedial exercises has been made adequate by brilliantly drawn diagrams. An admirable book. (E. & S. Livingstone Ltd., price 5s.)

Medical Terms, Their Origin and Construction, by Ffrangcon Roberts, M.D., F.F.R., has now appeared in a second edition. In these days, when the average medical student knows 'small Latin and less Greek', and has seldom more than a smattering of knowledge about his own language, this little book performs a most useful function. It should be in the hands of every medical student, and there are few practitioners who will not benefit from a perusal of its pages. (William Heinemann Medical Books Ltd., price 6s.)

Ratschläge für den Prostatiker und seinen Arzt, by Prof. Dr. Eduard Pflaumer, is a complete guide to the non-operative management of the enlarged prostate. It gives useful advice, intended for patients and general practitioners, on micturition, the passage of catheters, the avoidance of infection, and the treatment of residual urine. All the instructions given are clear, and the illustrations are well drawn and helpful. (Georg Thieme, price DM 3.75.)

Directory of District Nursing.—The Central Council for District Nursing in London has now published a supplement to its useful *Directory of District Nursing and Street Lists for London*. (25 Cockspur Street, London, S.W.1, price 1s. 6d.)

CORRIGENDUM.—The approved name for 'arfonad is trimetaphan, *not* verazide as was erroneously stated on p. 551 of our May issue.

THE PRACTITIONER: 50 Years Ago. See pages 707-708

In difficult situations, successful recovery depends largely on the countermeasures adopted. This is particularly so in dealing with many of the skin infections met with at this time of the year. ACHROMYCIN tetracycline is acknowledged to possess outstanding merits in controlling pyogenic infections of the skin and for the prevention of infection in wounds and abrasions. To the doctor it offers unsurpassed scope in antibiotic therapy of the skin . . . to the patient it promises assurance of speedy, uneventful recovery.

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combats the infection...hastens the recovery

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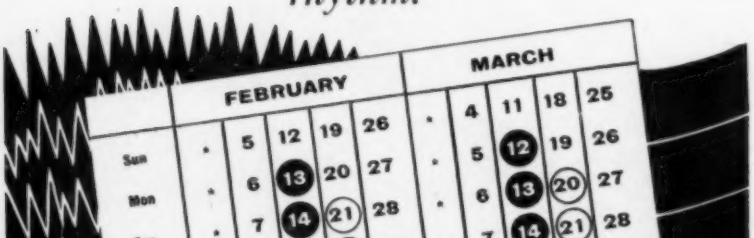

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THE PRACTITIONER
Fifty Years Ago

'Let there be gall enough in thy ink, though thou write
with a goose-pen, no matter'.—Shakespeare, *Twelfth Night*, Act *iii*, sc. 2, l. 52.

JUNE 1906

ONCE again the sky is red with the eloquence of irony and satire. Once again—to mix one's metaphors—the Editor is riding his favourite horse: 'Once again the International Medical Congress (at Lisbon) has come and gone, and once again it has passed like a ship in the night and left no mark on the sea of science. It was in some ways a fine pageant, and it is generally agreed that it was a pleasant picnic. It was abundantly evident that this was all most of the members wanted; the work was left to a few enthusiasts who took their pleasures sadly in telling each other what all knew beforehand they would say . . . Usually the attitude of the audience towards the orator of the moment was that of Falstaff towards the "old lord of the council", who talked very wisely, but he regarded him not. Conversation was general, the President and officers setting the example. The object was to get through the business as speedily as possible. The hours of "work" were nominally from 8.30 till 12; in reality the meetings did not begin till 9 or later, and were generally over by 11. In all the sections many whose names were down to read papers failed to put in an appearance; in some sections there was no one present but the officers; and one actually "ceased upon the midnight with no pain" during the Congress, no meeting at all being held on the last day. It is not surprising therefore, to learn that not a fraction of the communications on the programme were read even by title . . . The Portuguese showed a delicate sense of courtesy in keeping their own language in the background. The German element was not so "pushful" . . . and showed a disposition to fraternise. The English, on the other hand, held themselves aloof in an isolation, which may in their eyes have been "splendid", but which to others seemed ungracious'. 'Men go to the meetings (the Editor continues) largely not to learn . . . but to show themselves, and to impress on the public mind the fact that any charitable suggestions as to their professional extinction are, as Mark Twain said of the rumour of his own death, "greatly exaggerated". This is the microbe that lurks in all congresses'.

There is much also that is eminently quotable in the editorial comments on 'The Eternal Gullible', 'Faith Healing', 'Telephone Neuroses', 'The Sanitary Salute', and 'The Danger of Handshaking'. One penultimate extract from 'The Revolt of the General Practitioner' to conclude 'Notes by the Way' on an up-to-date note: 'A complaint very often heard from the general practitioner is that patients whom he sends to an operating surgeon are simply annexed by the latter. The patient is taken into a home, and the general practitioner knoweth him no more'. And lastly 'A Correction'—in the May 1905 issue it was stated that Sir Astley Cooper was appointed surgeon to Guy's Hospital in 1780. The famous surgeon was then only 12 years old. 'The "printer's devil" is a wayward sprite and delights in mischief'.

Charles Aston Key (1793-1849)

Now for the 'Original Communications'. W. E. de Korté, M.B., of the London Lock Hospital, concludes from 'prolonged search' that 'if the spirochæta pallida be the cause of syphilis, it does not exist as such in the blood', and he goes on to describe 'certain bodies

present in the chancre, in the condyloma, and in the blood during secondary syphilis'.

Frank E. Taylor, M.R.C.P., F.R.C.S., Pathologist to the Chelsea Hospital for Women, contributes an article on 'Necrobiotic Fibroids and Pregnancy' with striking illustrations by Bland-Sutton's favourite artists Charles Berjeau and Frank Butterworth: 'In a well-marked example, the cut surface of the tumour presents a homogeneous deep red colour, having quite lost its characteristic whorling. This appearance has suggested to the minds of various observers a resemblance to liver, or to raw beefsteak'.

G. H. Colt, M.B., late House-Surgeon, St. Bartholomew's Hospital, discusses 'The After-Treatment of Cases of Suprapubic Cystotomy'; R. Fullerton, M.D., of the Glasgow Royal Infirmary, reports the 'Removal of a Tracheotomy Tube which had become impacted in the left Bronchus'; and J. G. Turner, F.R.C.S., L.D.S., Dental Surgeon and Lecturer on Dental Surgery, Royal Dental Hospital of London, presents a 'Review of Dental Surgery'.

Aston Key, Thomas Bell, John Hilton, William Withey Gull (who 'left behind him what was probably the largest fortune ever made by the practice of medicine'), and Walter Moxon are commemorated in the second instalment of 'Some Great Men of Guy's'. Charles Aston Key (1793-1849), who is eponymously known for his lateral operation for lithotomy performed with a straight staff, and who introduced the principle of dividing the stricture outside the sac in a strangulated hernia, had his path to surgical advancement made easy by marrying Astley Cooper's niece. A post of assistant-surgeon at Guy's was specially created for him. A great operator with large powerful hands, he gained celebrity by successfully tying the subclavian artery for axillary aneurysm in 1823.

Among the books reviewed is 'Dietetics for Nurses' by Julius Friedenwald and John Ruhräh, first 'Clinical Professor of Diseases of the Stomach in the College of Physicians and Surgeons, Baltimore'.

'Alcohol in disease', according to the *Montreal Medical Journal* for November 1905, 'is a valuable food, replacing carbohydrates, and as a general rule saving proteid metabolism. It places no tax on the digestive organs; on the contrary, if used intelligently, it increases their secretion, thus, in low and asthenic conditions, assisting the digestion and favouring the absorption of other foods. In such conditions, it may also have a favourable action on the hepatic cells stimulating them to increased activity'.

'Practical Notes', discussing cirrhosis of the liver, state that 'The pure spirit, not much diluted and taken without food, is most conducive to this disease . . . It is generally believed that it is the fusel oil, which is the chief irritating element'. W. R. B.

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Vitamin A	5000 I.U.	Ascorbic Acid (C)	75 mg.
Vitamin D	500 I.U.	Niacinamide	20 mg.
Thiamine HCl (B_1)	3 mg.	Calcium pantothenate	1 mg.
Riboflavine (B_2)	2 mg.	Vitamin B_{12}	5 mcgm.
Pyridoxine (B_6) HCl	0.2 mg.	as present in concentrated extractives from streptomyces fermentation	

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MOTORING NOTES

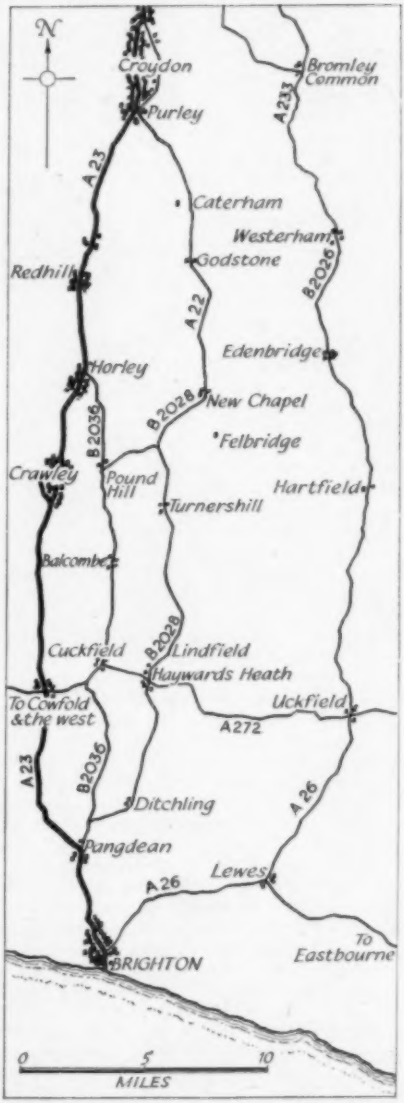
Avoiding Busy Roads

By ROBERT NEIL

It is surprising how many motorists adhere strictly to the busy main roads, usually infested with slow-moving lorry traffic and frequent 30 m.p.h. limits, and never seem to make the slightest effort to use the many alternative routes available. There are throughout the country alternative ways to nearly all the best known of the main arteries, and not the least benefit to be gained from using such roads is that it is often easier to find reasonable restaurants and hotels. It is said that N6 is the best fed road in France; it would probably be true to describe our own outdated A5 as the worst fed road in Britain. A little time spent studying the map occasionally will help any motorist to find that the shortest, quickest and pleasantest route is not always that which is regarded as the main road.

LONDON TO BRIGHTON

Many doctors will be travelling to Brighton for the B.M.A. meeting next month, and the first road that comes to mind is the London to Brighton Road, A23, which is typical of almost all that is worst; marred, as it is, by countless wayside cafes and garish advertising signs. For anyone starting from London itself it is difficult to avoid the main route as far as Purley, but here an alternative way is offered. I would suggest that instead of turning right on the main road through Redhill and Crawley, the road straight on, which leads eventually to Lewes, by way of Caterham and Godstone, should be taken. If, as sometimes happens, the traffic shows signs of increasing after Godstone another slight deviation can be used. At New Chapel, about four miles north of the junction with the Crawley road at Felbridge, the turning to the right on to B2028 should be taken. This road goes by way of Turners Hill, Haywards Heath and Ditchling to join the main Brighton road at Pangdean. During all normal motoring hours this route will be found both faster and pleasanter than the main road, and the countryside and scenery are much more attractive than those lining the main road. Even should it be necessary to use a portion of the main road through Redhill, much can be avoided with a little care. The turning on to B2036 should be taken at Horley, and this will lead through Pound Hill, Balcombe and Cuckfield to join the main road at Pangdean.



Perhaps the best available road to Brighton is that which goes by way of Westerham, Edenbridge and Uckfield, although this is most helpful to motorists starting their journey from south-east London, or even north of the Thames. In spite of the countryside in which it lies, this is one of the quietest roads in south-

eastern England, and because of this can be the quickest way to Brighton, Eastbourne or Lewes. This is certainly the road I would recommend to any motorist starting his journey to Brighton from north-east of London, and who must, inevitably, be faced with the necessity of crossing the river somewhere. It is best to time one's journey so that the Greenwich Tunnel can be used outside its busiest hours. After six in the evening most of the lorry traffic will have dispersed. Once the tunnel has been passed, the road through Blackheath, Kidbrooke and Bromley should be followed, and the last named should be left by the Sevenoaks road. On reaching Bromley Common A233 should be used, and this will lead on through Westerham, Edenbridge, Hartfield and Uckfield to Lewes and Brighton. In every way this is a better road than the infamous A23 further west.

There are probably many motorists who are forced to start a journey to Brighton from the north-west, and who may feel that the only way is to drive to London and then head south down the main road, with its dangerous processions of traffic. Those motoring from either the west or the north-west would be advised to pay particular attention to one of the least known roads in the country; little known because so many motorists have grown used to assuming that all roads radiate from London, or other big towns. The road I have in mind is that which runs from Battle, Sussex, in the east, to Winchester in Hampshire. During its length it passes through Uckfield, Cowfold, Billingshurst, Petworth and Petersfield. It can easily be seen how useful this road can be to motorists driving towards Brighton from the west of London. Radiating from Winchester are roads which lead to Bournemouth, Salisbury, Marlborough, Hungerford and Newbury, which allow motorists from many points of the compass to make use of this excellent way.

Motorists who live almost due north of London, and who might hesitate to use the Thames tunnels or ferries, can still avoid the complications of motoring through London. Although the North Circular Road round London is now little more than an example of the way in which weakness has allowed arterial roads to become strip housing schemes, there are alternative orbital ways all round London if an effort is made to check them first on the map. One great advantage of these orbital ways is that they can be joined at whichever point suits the individual driver. The innermost circle likely to be of use is that following a line through Bishops Stortford, Ware, St. Albans, Rickmansworth, Windsor and Ascot, whilst farther out from London the road which follows Royston, Baldock, Hitchin, Dunstable, Aston Clinton and along the Icknield Way by Wallington to Reading and the south can be equally useful.

ROUTES TO AND FROM THE NORTH

Many motorists find the initial stages of leaving London on A1—the so-called Great North Road—extremely irritating. To avoid it I use that famous old coaching road A10, which can be joined at many places, but the most convenient way for most motorists would be to head for Enfield, and so join the Cambridge Way to Cheshunt and Ware, to Buntingford, Royston and Godmanchester and to rejoin the North Road at Alconbury Hill, just south of Stilton. This is not only a fast road, but one pleasantly free from lorry traffic, that curse of most main roads. Once Alconbury Hill is reached many of one's worries are left behind, but if the target for the night is far north there are still the irritations of Stamford, Grantham and Doncaster to be dealt with. There are many drivers who consider that it is not possible to avoid these towns, but it can be done with relative ease.

Just north of Stilton, at Norman Cross, the turning to the right leading to Peterborough should be taken. After Peterborough, A15 should be followed through Bourne and Sleaford to Lincoln, and then up Ermine Street to Brigg. Here the left turning should be taken, and the road followed through Scunthorpe, Thorne and Snaith, to rejoin the North Road at Ferrybridge. Although this route is slightly longer than by A1, under average conditions it will be slightly faster, with the added benefit that the maddening queues in Stamford and Doncaster will have been avoided.

An equally useful road, to be used as a variation from the Great North Road, is that which leads through the Dukeries. Coming from the north the main road is left just south of Bawtry, and A614 is followed through Ranby and Ollerton until a few miles south of the crossing of the main road between Newark and Mansfield. Here a left turn on to B688 will lead one on to the Fosse Way—A46—which leads to Leicester. This route can be used to reach other destinations if it is left by A606 so as to join the road through Melton Mowbray and Market Harborough to Northampton. Study of a good map will immediately suggest other ways in which this road can be used. If the turning to the south-west is taken in Market Harborough, on to B4036, this will lead through West Hadden and Daventry to Banbury and Chipping Norton. It can be seen that this route from Bawtry which I have described could easily be adapted for use as a road to Brighton for practitioners coming from the north-east, or beyond.

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The practitioner frequently encounters circumstances when that "something" is likely to be the vitamin B-complex. Administration of antibiotics, acute infections, surgery of the alimentary tract are particularly associated with impaired absorption or utilisation of these essential factors, with resultant insufficiency.

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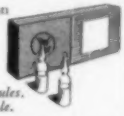

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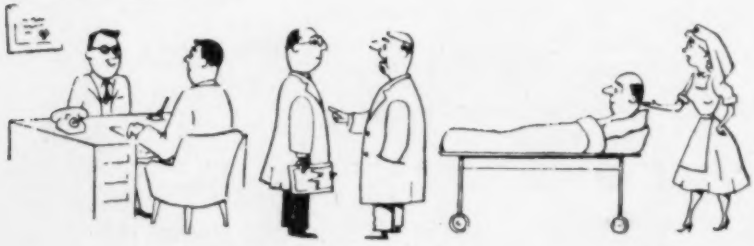

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Calorific value			
	per oz.	129	16.1
	per 100 grms.	457	57.1
Vitamin D	per oz.	320 i.u.	
	per pint		800 i.u.
Calcium	per oz.	260 mgms.	
Phosphorus	per oz.	200 mgms.	
Iron	per oz.	1 mgm.	

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		Dry Food	Reconstituted Food (1 in 10)
Fat		12.0%	1.2%
Protein		11.5	1.2
Lactose		16.5	1.6
Cane Sugar		55.5	5.5
Mineral Salts		3.0	0.3
Moisture		1.5	90.2
Calorific value			
	per oz.	128	12.8
	per 100 grms.	454	45.4
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	per pint		640 i.u.
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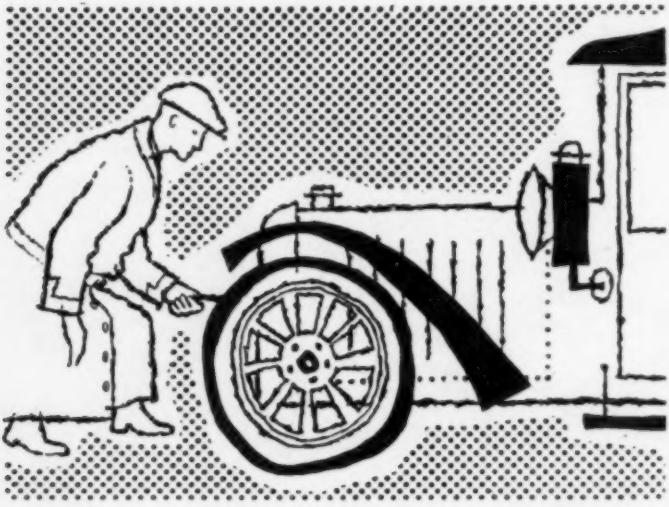

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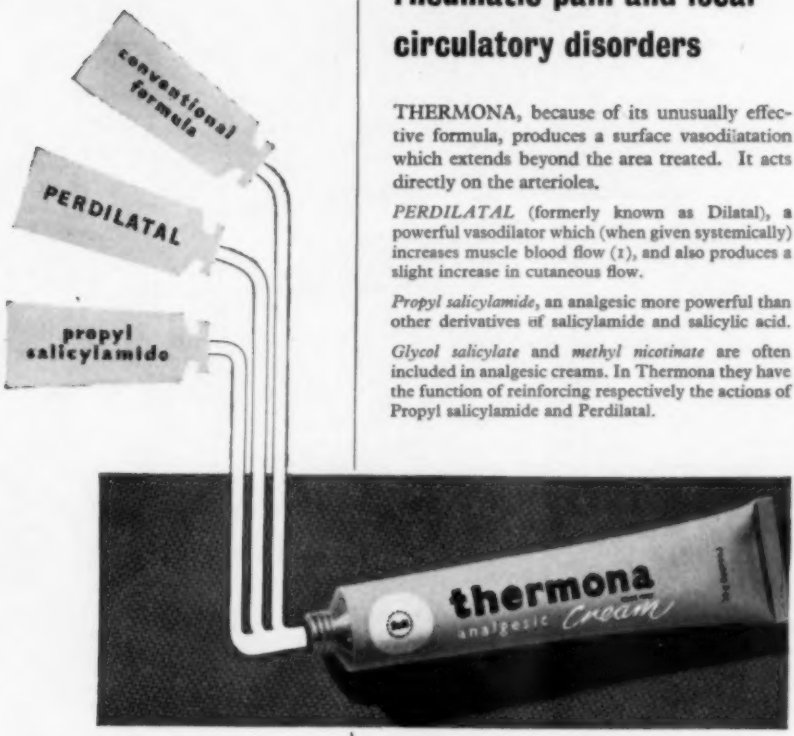

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Methyl nicotinate ..... 1·0%
Glycol salicylate ..... 10·0%
Vanishing cream base .... 83·7%

(1) Walder, D.N. *Lancet*, 1956, *1* 257.

INDICATIONS

(1) The group of conditons covered by the terms 'muscular rheumatism' and 'fibrositis'.
(2) Local circulatory disorders where they have surface manifestations (e.g. chilblains, Raynaud's disease).

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Proc. Soc. exp. Biol. N.Y. (1954) 86: 120.

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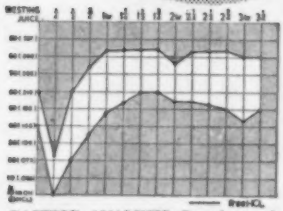
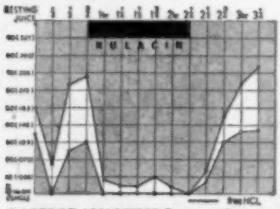


GASTRIC ANALYSIS Superimposed gruel fractional test-meal curves of five cases of duodenal ulcer



GASTRIC ANALYSIS Same patients as in Fig. 1, two days later, showing the striking neutralizing effect of sucking Nulacin tablets (3 an hour). Note the return of acidity when Nulacin is discontinued.

In the past, the successful treatment of many cases of peptic ulceration demanded hospital conditions. Now, by means of Nulacin Tablets, it is possible to control gastric hyperacidity without any inconvenience to the patient. By using Nulacin Tablets as directed, an ambulant patient can obtain all the advantages of intragastric milk-alkali drip therapy.

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FURTHER RESEARCH has now been done into the irritant effects of aspirin upon the gastric mucosa. A detailed report on this work appears under the heading "Aspirin and Ulcer" in the B.M.J., July 2, 1955.

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"Aspirin is a serious gastric irritant, particularly in peptic ulcer patients."

Here is a further extract from the report:—

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[1] *Practitioner* (1954). Vol. 172, p. 183.

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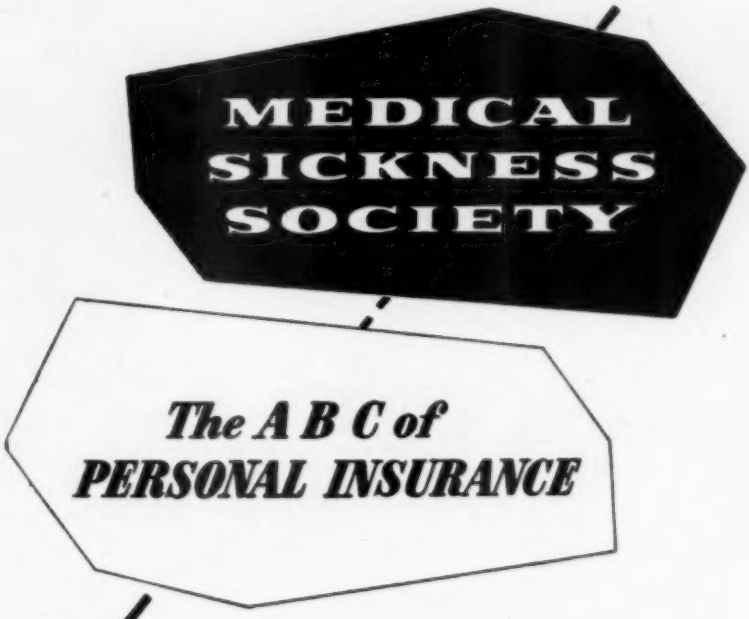

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